The impact of radiation therapy on thyroid function in patient with head and neck tumors

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ABSTRACT

Background: Head and neck cancers (HNC) accounted 1,518,133 new cases of all sites of HNC with 510,771 new deaths. The first reports on hypothyroidism following RT for HNC were published in the 1960s. The study aimed to determine the incidence of thyroiditis in patients with HNC, to estimate impactions of radiation of thyroid function in neck irradiation and to determine radiotherapy dose-volumetric threshold of radiation-induced hypothyroidism in HNC.

Methods: A prospective study of 35 patients with HNC treated with IMRT-VMAT were studied. Data were collected when reviewed of medical record of patient. The variables were studied: age, gender, comorbidity, site of primary tumors, histopathology, surgical margin resection, dose of RT, V40, 50, 60(cm^3) of thyroid gland, 95%dose received by thyroid, mean dose, minimum and maximum doses. Thyroid assessment done by ultrasonography of neck after radiotherapy (RT). Thyroid function determined by TFT tests (TSH, free T3 and free T4) were done at baseline before treatment and after RT for each case.

Results: In this study, the mean age was 57.71±11.43 yrs., males were (24, 68.6%), whereas females were (11, 31.4%). Among site of primary cancer, 7(20.0%) of cases were tongue, NPC (5, 14.3%), and larynx (12, 34.3%). 30 of cases were SCC (85.7%). The most frequent doses used were 6600cG. Regarding TSH, the results showed that postRT had greater mean level of TSH than pretreatment, with a high significant difference (P= 0.009). Regarding fT3, the results showed that postRT had lesser mean level of fT3 than pretreatment with a high significant difference (P= 0.007). Regarding fT4, the results showed that postRT had lesser mean level of fT4 than pretreatment with a high significant difference (P= 0.015). The mean total dose received by thyroid gland was 4170.13±983.38 cG (median= 4172.5 cG). In addition, the mean 95% dose was 6.8 Gy (median= 4 Gy). The volumes of gland at V40, V50 and V60 were 79.47±28.69 cc, 39.28±19.81 cc, and 38.02±23.83cc, respectively. The incidence of hypothyroidism was (14.3%) and Euthyroid incidence rate was (85.7%).

Conclusions: RT doses more than 66 Gy is highly associated with the incidence of hypothyroidism. fT3 and fT4 has be dropping postRT to HNC whereas TSH is raising. In dosimetry, the mean total dose received by thyroid gland is 4170.13±983.38 cG. The mean 95% dose was 6.8 Gy (median= 4 Gy). The volumes of gland at V40, V50 and V60 are 79.47±28.69 cc, 39.28±19.81 cc, and 38.02±23.83cc, respectively. The incidence of hypothyroidism is (14.3%) and euthyroid incidence rate is (85.7%).

Keywords: hypothyroidism, HNSCC, Euthyroid, IMRT-VMAT, thyroid

INTRODUCTION

The thyroid gland is the largest pure endocrine gland in humans. It is secret two main thyroid hormones (triiodothyronine; T3 and thyroxine; T4) are crucial in normal growth and development, overall energy expenditure and substrate utilization [1, 2].

In 2021, HNC accounted for a substantial proportion of the entire cancer burden globally, with 1,518,133 new cases of all sites of HNC with 510,771 new deaths [3]. In that year in Iraq, there were 2,734 new cases of HNC and 909 deaths from HNC [4].

Radiation effects on the thyroid gland were first reported in the 1920s in thyrotoxic patients administered RT. The first reports on hypothyroidism following RT for HNC were published in the 1960s [2].

Nowadays, RT is widely used in the management of HNC, lymphomas and malignancies of the central nervous system. Due to scattered irradiation, complex anatomy and inadequate selectivity of RT techniques, exposure of non-target organs during RT of the head and neck areas is unavoidable [2].

The probability of hypothyroidism after RT is in the range 7.5–38%, depending on the population and dosage [5-10]. Patients with NPC seem to have a higher risk of hypothyroidism than patients with any other type of head or neck squamous cell carcinoma, because of differences in the RT field and dosage [11]. Laryngeal and hypopharyngeal cancer, as well as laryngectomy, which occur in close proximity to the thyroid gland, are thought to lead to hypothyroidism after RT [6, 12].

Many advances have been achieved in the understanding of the biology, natural history, treatment of HNC and side effects. The incidence of hypothyroidism varies with tumor stage, surgery type, radiation dose to the thyroid, concurrent chemotherapy administration, and preexisting thyroiditis [13]. Hypothyroidism has been noted in about 30% when the thyroid gland received doses >45 Gy, particularly when concurrent chemoradiation was administered [14, 15]. Bhandare et al. [16]

reported that when the dose to the gland was >45 Gy, the incidence of hypothyroidism increased from 60% to 76% at 5 years.

Despite a relatively high number of both animal and human studies, clear-cut data on the incidence, type, pathophysiology and severity of radiotherapy-induced thyroid dysfunction are scarce and inconsistent [2]. The differences in radiotherapy volumes, doses, fractionation schemes, and techniques, application of other treatment modalities like concurrent chemotherapy, the extent of surgery, and differences in the frequency and adequacy of follow-up evaluation, inconsistent definitions of thyroid disorders (for example, clinical and/or biological hypothyroidism) and other factors [2, 6-8].

The study aimed to determine the incidence of thyroiditis in patients with HNC, to estimate impactions of radiation of thyroid function in neck irradiation and to determine radiotherapy dose-volumetric threshold of radiation-induced hypothyroidism in HNC.

METHODS

Study Design and Setting

A prospective study of 35 patients with HNC treated with IMRT-VMAT were studied. The demographic data, the primary tumor details and radiotherapy information were recorded. The study conducted in Baghdad Radiotherapy and Nuclear Medicine Center, Baghdad Medical City-Complex, Baghdad, Iraq, in period between December 2023 and May 2024.

Data collection

Data were collected when reviewed of medical record of patient. The variables were studied: age, gender, comorbidity, site of primary tumors, histopathology, surgical margin resection, dose of RT, V40, 50, 60(cm^3) of thyroid gland, 95%dose received by thyroid, mean dose, minimum and maximum doses.

Inclusion criteria

a) Any pathology proven HNC: Tongue, Ear (Glomus, paraganglioma), Larynx (Glottic, supraglottic), Check, Maxillary sinuses, NPC, Oral cavity, Palate (hard), Parotid, Salivary gland, Tonsils and Skin (BCC).
b) Patients with involvement of the thyroid gland
c) Locoregional of neck lymphatic RT fields.
d) Normal thyroid function (euthyroid) before RT.

Exclusion criteria

a) Primary tumors extending to any part of the H-P axis and those with preexisting pituitary or thyroid disease.
b) Untreated lower neck LNs.
c) Previous RT to the neck.
d) Thyroid surgery.
e) Radio-Iodine therapy.
f) Loss for follow-up patients.

Ultrasonography of thyroid

Thyroid assessment done by ultrasonography of neck after RT, to detect any abnormal findings like nodule lesion and changes in echogenity.

Investigations

Thyroid function determined by TFT tests (TSH (NR= 0.34-4.25 mlU/L), free T3 (NR= 2.1–3.8 ng/dl), and free T4 (NR= 0.82–2 ng/dl)) were done at baseline before treatment and after RT for each case. Hypothyroidism is defined as a TSH value greater than upper limit of normal. The time to onset of hypothyroidism was defined as the interval between the end of radiotherapy and the first recorded abnormal TSH laboratory value [17].

CT Simulation

Patients were immobilized with a thermoplastic head-and-neck mask that included the shoulders to ensure reproducibility of radiotherapy. CT simulation was performed in all patients, and the patients were planned. Thyroid gland was contoured manually on CT images, and the absolute thyroid volume, dose–volume histograms (DVHs), and percentage of thyroid gland volume absorbing RT dose were determined. Ideally, CT slices should be 3 mm (but no more than 5 mm) thick to aid accurate target volume definition [18].

RT technique

Dose volume histograms were created for all treatment plans and all dosimetric data were transferred to VMAT radiotherapy planning system. Treatment was performed with photons linear accelerator. All patients received RT with 2 Gy daily fractions. The different dose-volume parameters including the mean, maximum and minimum doses to the thyroid gland, mean thyroid volume and the thyroid volumes were analyzed from the DVHs.

Statistical analysis

Study data were collected and processed using electronic data from the view capture tools (Monaco® Electa HP version 5) and statistical analysis was performed using SPSS v24 (IBM Inc., Chicago, IL, USA). Descriptive statistics consist of numbers, and percentages were measured. Mean, median, range, min, max, and SD for categorical data calculated. An association between variables TFT assessed by an unpaired t-test. A two-sided *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Patients' baseline variables

The mean age was 57.71±11.43 yrs, and it was ranged from 17 yrs to 80 yrs (median = 60 yrs). In relation to sex, males were (24, 68.6%), whereas females were (11, 31.4%). Regarding comorbid condition, we recorded 3(8.5%) of cases were DM, 12(34.3%) of case with HTN, and 2(5.8%) of patients were mixed, as listed in (Table 1).

Table 1. Patients distribution according to demography (No.=35).

Variables		No.	%
Age (years)	0-20	1	2.9
	21-40	2	5.8
	41-60	18	51.4
	>60	14	40.0
Sex	Male	24	68.6
	Female	11	31.4
Comorbid	DM	3	8.5
	HTN	12	34.3
	DM+HTN	2	5.8
	Absent	18	51.4

Tumor variables

Regarding site of primary cancer, 7(20.0%) of cases were tongue, NPC (5, 14.3%), and larynx (12, 34.3%). Regarding to histopathology, 30 of cases were SCC (85.7%), while the rest reported as follow: two-case mucoepidermoid, two-case vascular tumor, and one-case adenocarcinoma. According to surgical treatment, 13 of cases were done (37.1%), while not done in (22, 62.9%). In the current study, the RT doses ranged from 4500cG to 7000cG. The most frequent doses used were 6600cG in 14(40.0%), (Table 2).

Table 2. Patients distribution according to tumors (No.=35).

Variables		No.	%
Site	Tongue	7	20.0
	Ear (Glomus, paraganglioma)	2	5.8
	Larynx (Glottic, supraglottic)	12	34.3
	Check	1	2.9
	Maxillary sinuses	1	2.9
	NPC	5	14.3
	Oral cavity	1	2.9
	Palate (hard)	1	2.9
	Parotid	1	2.9
	Salivary gland	2	5.8
	Tonsils	1	2.9
	Skin (BCC)	1	2.9
Surgical treatment	Yes	22	62.9
	No	13	37.1
Histology	Adenocarcinoma	1	2.9
	SCC	30	85.7
	Mucoepidermoid	2	5.8
	Vascular tumor	2	5.8
RT doses	63	7	20.0
	60	8	22.9
	66	14	40.0
	70	3	8.6
	Other	3	8.6

Thyroid assessment

Thyroid assessed by ultrasonography (US) of neck pre and post radiotherapy (RT). All cases had normal preRT US. PostRT, most of cases presented with normal findings (30, 85.7%), while abnormal signs recorded as follow: Hypoechoic nodule (2, 5.7%), and Isoechoic nodule (3, 8.6%), as shown in (Table 3).

Table 3. PostRT US of thyroid gland.

Finding	No.	%
Hypoechoic Nodule	2	5.7
Isoechoic Nodule	3	8.6
Normal	30	85.7
Total	35	100.0

In relation to the thyroid function tests (TSH, fT3, fT4), the findings listed in table 3.4. Regarding TSH, the results showed that patients postRT had greater mean level of TSH (18.57±9.79 μIU/mL) than pretreatment (2.58±2.18 µIU/mL), with a high significant difference (*t*= -2.755-, 95%CI= 1.99-13.21, P= 0.009), (Figure 1).

Regarding fT3, the results showed that patients postRT had lesser mean level of fT3 (1.97±0.79 pg/ml) than pretreatment (2.49±0.48 pg/ml), with a high significant difference (*t*= 2.875, 95%CI= 0.15-0.88, P= 0.007), (Figure 2). Regarding fT4, the results showed that patients postRT had lesser mean level of fT4 (0.97±0.39 ng/dl) than pretreatment (1.61±1.44 ng/dl), with a high significant difference (*t*= 2.552, 95%CI= 0.13-1.15, P= 0.015), (Figure 3).

Table 4. TFT levels pre and postRT.

TFT	PreRT	PostRT	Unpaired test	95%CI	P value
	Mean ±SD (median)				
TSH (µIU/mL)	2.58±2.18 (1.64)	18.57±9.79 (3.4)	-2.755-	1.99-13.21	0.009
fT3 (pg/ml)	2.49±0.48 (2.5)	1.97±0.79 (2.28)	2.875	0.15-0.88	0.007
fT4 (ng/dl)	1.61±1.44 (1.27)	0.97±0.39 (0.98)	2.552	0.13-1.15	0.015

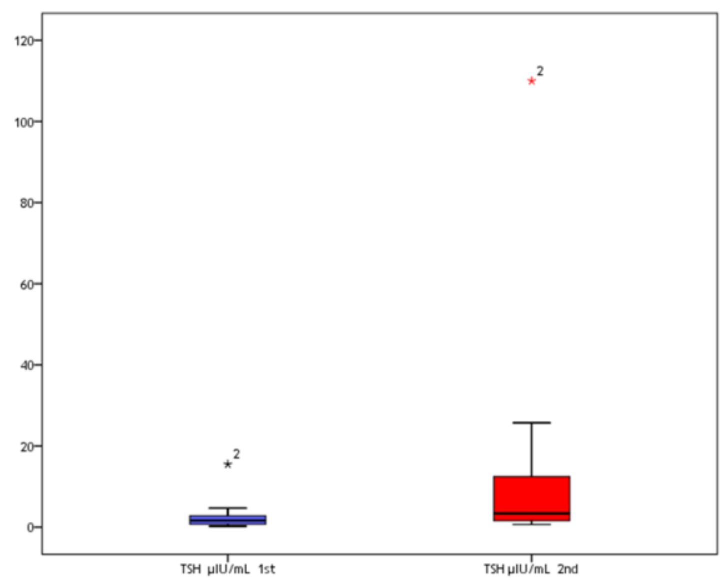

Figure 1. Boxplot of TSH concentration among patients pre and postRT.

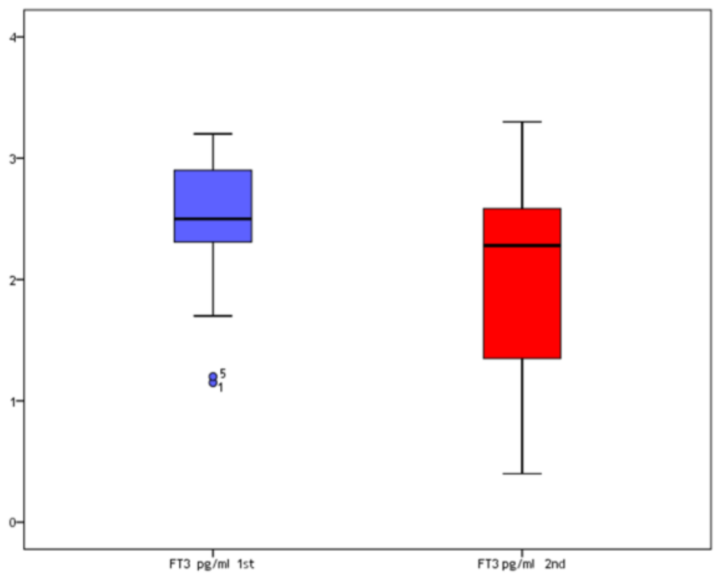

Figure 2. Boxplot of fT3 concentration among patients pre and postRT.

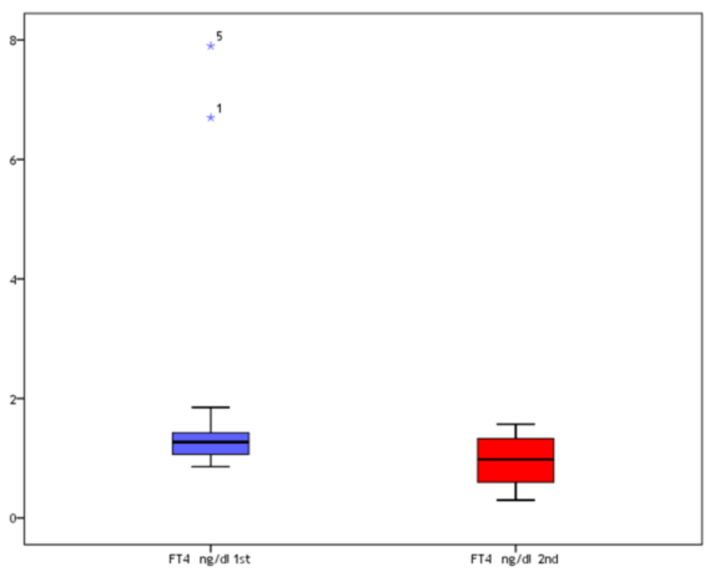

Figure 3. Boxplot of fT4 concentration among patients pre and postRT.

Thyroid and radiotherapy

In this study, the mean total dose received by thyroid gland was 4170.13±983.38 cG (median= 4172.5 cG). The mean of minimum dose was 3995.6±984.23 cG (median= 4051.0 cG). The mean of maximum dose was 5903.3±469.7 cG (median= 6000.0 cG).

In addition, the mean 95% dose was 6.8 Gy (median= 4 Gy). The volumes of gland at V40, V50 and V60 were 79.47±28.69 cc, 39.28±19.81 cc, and 38.02±23.83 cc, respectively, as listed in (Table 5).

Table 5. Parameters of doses of RT received by Thyroid gland during HNC RT.

Parameter	Mean dose (cG)	Minimum dose (cG)	Maximum dose (cG)	V 40 (cc)	V 50 (cc)	V 60 (cc)	Dose received at 95%
Mean	4170.13± 983.38	3995.6± 984.23	5903.3± 469.7	79.47±28.69	39.28±19.81	38.02±23.83	6.8
Median	4172.5	4051.0	6000.0	85.0	40.5	45.0	4
Minimum	2515	2500	4400	0.45	0.24	0	0
Maximum	6288	5600	7268	100.0	100.0	71.0	25

Hypothyroidism

In this study, the incidence of hypothyroidism was (14.3%). Euthyroid incidence rate was (85.7%), shown in (Table 6). The hypothyroidism cumulative incidence shown in (Figure 4).

Table 6. The incidence of hypothyroidism and euthyroid in this study.

Thyroid status	No.	%
Hypothyroidism	5	14.3
Euthyroid	30	85.7
Hyperthyroidism	0	0

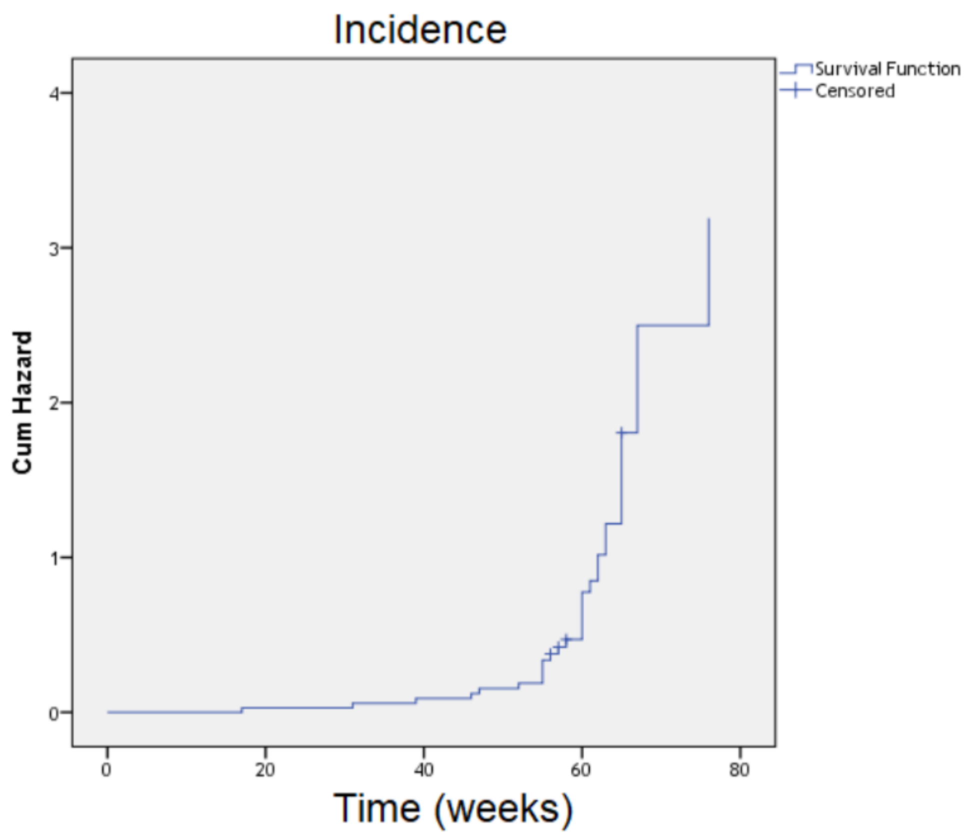

Figure 4. Cumulative incidence of hypothyroidism.

DISCUSSION

Different studies confirmed that external 3DCRT for HNC can caused hypothyroidism [60-64]. In the current study, the mean age of patients was 57.71±11.43 yrs, with median of 60 yrs. Many papers reported same findings [15, 19-24]. Tell et al, recorded that their cases ages ranged from 21-94 yrs (median, 65 yrs) [19]. Diaz et al, studied 144 patients with mean age of 56.9 ys received [15]. El-Shebiney et al, [23] recorded that the median age at diagnosis was 60 (range; 42–76) years in Egyptian individuals. This could be explained by small sample collected in this study and different localities between countries.

In 2023, Ritlumlert and co-authors studied 220 NPC cases. Their mean age was 48.28±11.71 yrs (18-83 yrs) with the majority being male (72.27%). Most cases were of clinical staged 3(51.82%), N stage 2(51.82%), and T stages 2 or 1 (33.18% and 31.36%, respectively). Two pre-treatment clinical variables, the level of TSH and the thyroid volume, were significantly different between the patients. They found no significant difference in dosimetric variables between the groups of the study [25].

In relation to gender, males were (24, 68.6%), whereas females were (11, 31.4%). Similar to the study of Tell et al, 231(75%) males and 77(25%) females [19] and Bhandare et al, 200(64%) men and 112(36%) women [26]. While El-Shebiney et al, studied 78 HNSCC patients (51% males and 49% females) [23]. The correlations of post-RT hypothyroidism with sex, thyroid volume, age, tumor stages, or sites in some studies, indicate a higher incidence of hypothyroidism among female patients [15, 24], whereas other studies show no impact on the likelihood of developing hypothyroidism on the basis of gender [19, 26-28]. Another study suggested that thyroid volume in female seem to be associated with thyroid toxicity [29], because women do have a smaller thyroid volume than men. In Diaz et al, analyzed thyroid volumes with controls for gender and determined that volume was indeed a risk factor, demonstrating an increased risk associated with smaller thyroid volumes in female gender [15].

Regarding co-morbid conditions, we recorded 3(8.5%) of cases were DM, 12(34.3%) of case with HTN. A similar findings observed in Bhandare et al, documented one case of the 13 patients with DM who received low neck node treatment developed clinical thyroiditis, and 2/15 patients developed subclinical status without any significance between DM and thyroiditis. However, DM was significant for subclinical thyroiditis ($p= 0.041$) [26]. In addition, El-Shebiney et al, found 44.9% of HNSCC cases had DM (6.4%) or HT (28.2%) or both (10.3%) [23]. Similar to Pal et al, [30] studied 95 HNSSC cases, most of them (80.3%) were males. Nine cases had hypertension and three had DM.

Regarding site of primary tumor, 7(20.0%) of cases were in tongue, NPC (5, 14.3%), and larynx (12, 34.3%), where 11 case found in different sites. All previous studies documented different primary site of HNC like Tell et al, reported 25 patients of hypopharynx, 92 cases of larynx, 11 cases of NPC, 67 cases of oral cavity, 72 cases of oropharynx, 14 cases of major salivary glands and 27 CUP (unknown) [19]. Whereas, Bhandare et al, studied 56 cases of nasal cavity SCC, 119 cases of NPC, 100 cases of sinusal cancer, and 37 cases of CUP [26]. Also, El-Shebiney et al, reported 21.8% NPC, 44.9% larynx and 33.3% oral cavity [23]. Pal et al, [30] studied larynx (35.2%), oral cavity (19.7%), oropharynx, and hypopharynx (15.5% each).

Regarding to histopathology, 30 of cases were SCC (85.7%), while the rest reported as follow: two-case mucoepidermoid, two-case vascular tumor, and one-case adenocarcinoma. According to surgical margin resection, 13 of cases were negative (37.1%), while positive found in (22, 62.9%). In the current study, the RT doses ranged from 4500cG to 7000cG. The most frequent doses used were 6600cG in 14(40.0%). These data dislike most previously studies [15, 19-23], whom reported that the majorities of cases were SCC. El-Shebiney et al, [23] studied 78 cases of head and neck cancer, all are SCC.

Some studies found no association between hypothyroidism and age, sex, radiation dose or fractionation, T and N stage, tumor site, and neck dissection [15, 19, 27, 28]. El-Shebiney et al, [23] found that 37.2% of patients underwent complete surgical interventions. In Tell et al, study 150 patients underwent surgery. Thirty-four patients (11%) underwent surgery that involved the thyroid gland, and 124 patients (40%) exposed to non-thyroidal surgery [19].

In the present study, all cases had normal preRT US. PostRT, most of cases presented with normal findings (30, 85.7%), while abnormal signs recorded as follow: Hypoechoic nodule (2, 5.7%), and Isoechoic nodule (3, 8.6%).

In addition, Tell et al, found that 17% of patients were diagnosed with overt hypothyroidism postRT [19]. Pal et al, [30] studied reported the incidence of hypothyroidism was 29.6% and concluded that primary site, sex, and the beam used in the treatment did not show any defining role.

Several authors concluded that irradiation of the complete or partial thyroid and the dose–volume distribution in the irradiated thyroid gland has been thought to influence the incidence and intensity of hypothyroidism [14, 15, 26]. Other reported a co-relationship between the volume of thyroid radiated and the incidence of thyroiditis, suggested that the % of volume receiving >30Gy (V30) is a possible predictor of disease and significantly affects the peak level of serum TSH [31].

Data from Bhandare et al, study suggested a possible dose–volume effect of an elevate in the incidence of hypothyroidism with an increase in the thyroid volume >50% receiving greater radiation doses [26]. In our study, the mean total dose received by thyroid gland was 4170.13±983.38 cG (median= 4172.5 cG). The mean of minimum dose was 3995.6±984.23 cG (median= 4051.0 cG). The mean of maximum dose was 5903.3±469.7 cG (median= 6000.0 cG). Similarly, El-Shebiney and colleagues documented the mean thyroid volume of 12.84 ± 3.75 cc, and mean thyroid dose was 3357.47 ± 1218.26 cGy [23]. Also, Pal et al, [30] calculated nearly the same findings. The volume of the thyroid varied from 4.9 cc to 30 cc, with a median volume of 11.37 cc. The maximum dose received to a point varied from 4,810 cGy to 7,597 cGy, and the mean dose varied from 596 cGy to 6,827 cGy.

Bhandare et al, reported 40 patients developed clinical hypothyroidism. 13(25%) developed subclinical hypothyroidism. 50% none developed clinical thyroiditis. However, one patient (10%) developed subclinical thyroiditis [26]. Some studies suggest that the incidence of hypothyroidism depends on the total dose to the thyroid [15].

In present study, the mean 95% dose was 6.8 Gy (median= 4.0 Gy). The volumes of gland at V40, V50 and V60 were 79.47±28.69 cc, 39.28±19.81 cc, and 38.02±23.83 cc, respectively. Recently, many studies found that IMRT with thyroid constraints has a statistically significantly lower percentage of thyroid treated at V20, V30, V40, and V50, as well as a lower median dose than IMRT without thyroid constraints ($p< 0.0001$). 3DCRT produced a lower V10, V20, and V30 and a higher V60, as well as a lower minimum, maximum, and median radiation dose than IMRT without thyroid constraints ($p< 0.05$). As comparison, contouring the thyroid as an IMRT avoidance structure results in a significantly lower median thyroid dose ($p= 0.007$) but a significantly higher minimum and maximum dose ($p = 0.0001$ and 0.0004). Additionally, 3DCRT resulted in a lower V10 but a higher V30, V40, and V50 than IMRT with thyroid constraints among patients of the same gender, stage, and age ($p< 0.0001$, $p= 0.0012$, $p= 0.0001$, and $p= 0.0057$, respectively) [15, 26].

Pal et al. [30], used univariate and multivariate analysis of the DVH of the thyroid gland, volume receiving 50 Gy (V50), dose received to 50% volume D50), and the mean dose were found to be significantly associated with hypothyroidism. V10, V20, V30, V40, V45, V60, and the maximum point dose were not found to be significant.

The volume of irradiated thyroid seems to be a risk factor, given than hypothyroidism is more common if the height of the radiation field was more than seven cm [24]. Another study has shown that hypothyroidism is less common if less than half of the thyroid bed was irradiated, and the incidence increases with doses exceeding 50Gy along the irradiated volume [32]. There was a significant increase in the development of hypothyroidism after treating bilateral neck vs. unilateral neck [19]. If the entire thyroid volume is irradiated, the 5-year risk of clinical hypothyroidism is estimated to be 8% with 45Gy; 13% with 60Gy; and 35% with 70Gy [15]. On the basis of these estimates, the incidence of hypothyroidism could be reduced by decreasing the irradiated volume of gland or by reducing the size of field [32].

El-Shebiney et al, [23] used univariate analysis of the impact of different dose volumetric parameters on the development of post-radiotherapy thyroiditis showed that the minimum, maximum and mean doses of RT were significantly higher in the hypothyroid patients. Also, hypothyroidism was significantly associated with V10-V50 results.

In the present study, the incidence of hypothyroidism postRT is 14.3%. In India, Aich et al. [33] recorded an incidence of 21.8%, Srikantia et al. [34] 42.2%, and Laway et al. [35] 16.94% of hypothyroidism post conventional EBRT whereas Murthy et al. [36] which showed an incidence of 51% after IMRT. Gupta et al. [37], calculated the incidence of hypothyroidism, respectively, in 8%, 13%, and 35% postRT when the doses received were 45 Gy, 60 Gy, and 70 Gy, respectively.

These discrepancy in percent could explain by the thyroid gland is composed of multiple independent subunits, it is a parallel organ (i.e. the maximum point dose, and volume are play a significant role in determining the outcome postRT) [30].

Some authors divided hypothyroidism according to the dose volumes received by gland during RT fractions. Alkan et al. [38] reported that the dose received by the whole gland is a significant risk factor. Bhandare et al. [26] reported that if the treated volume was more than 85% (the chance of developing hypothyroidism was 23%). Alterio et al. [65] did not find any relationship between the irradiated thyroid volume and dose with respect to V10, 30 and 50.

A prospective study examining the role of DVH in head and neck carcinoma patients by Boomsma et al. [39] showed higher mean thyroid gland dose and decreased thyroid gland volume was the best fit for the Normal Tissue Complication Probability (NTCP) model of radiation-induced hypothyroidism.

In a study of dosimetric analysis, Akgun et al. [40] found that V30, thyroid volume, and D_{mean} were correlated to hypothyroidism in univariate analysis but none in multivariate analysis. On the other hand, Kim et al, [41] found that V35–V50, as well as the mean RT dose were significant predictors for radiation-induced thyroiditis. Cella et al. [42] reported that the V30 was a significant predictor for developing hypothyroidism after sequential CRT, although, these mentioned data supporting our findings.

Although the development of thyroiditis after doses as low as 20Gy has been reported, and after 30-45 Gy has been more commonly documented [26]. Jereczek-Fossa et al, inferred that the relative risk of thyroiditis increased by a factor of 1.02/Gy of radiation [43]. Similarly, Bhandare et al, reported that of the 312 patients, 190 were treated with once-daily fractionation at 1.36-2.0 Gy/fraction and 122 received twice-daily fractionation at 1.1-1.2 Gy/fraction. In addition, 40 patients received adjuvant chemotherapy: 17 received induction; 6, concomitant; 11, maintenance; and 6, combined chemotherapeutic schedules [26].

In the last decade the diagnostic strategy for using TSH measurements has changed as a result of sensitivity improvements in these assays, and it was recognized that serum TSH measurement is a more sensitive test than serum T4 for detecting borderline hypothyroidism or hyperthyroidism [44, 45]. In this study, the results of TSH showed that patients postRT had greater mean level of TSH (18.57±9.79 μIU/mL) than pretreatment (2.58±2.18 μIU/mL), with a high significant difference (P= 0.009). Regarding T3, the results showed that postRT had lesser mean level of T3 (1.97±0.79 pg/ml) than pretreatment (2.49±0.48 pg/ml), with a high significant difference (P= 0.007). Regarding T4, the results showed that patients postRT had lesser mean level of T4 (0.97±0.39 ng/dl) than pretreatment (1.61±1.44 ng/dl), with a high significant difference (P= 0.015). A disagreements were reported with previous studies [15, 20-24, 26], they found that hormones level could be influenced by RT. Furthermore, these are dislike with Tell et al, [19] used Cox regression analysis in the univariate analyses for continuous factors, found the pre-RT TSH value was a significant factor as an increased initial TSH value was a strong risk factor for hypothyroidism ($p<0.001$). Also, they concluded if RT to the neck was given as bilateral treatment, it was also a significant risk factor ($p= 0.02$) [19].

The 5-year and 10-year actuarial estimate for DFS of hypothyroidism for those underwent neck RT was 68% and 67%, respectively [26]. Tell et al, reported a cumulative number of hypothyroidism cases after 1, 3, 5 and 10 years was 20, 46, 49, and 52, respectively. This correspond to 38%, 88%, 94%, and 100% of the total risk to the development of thyroiditis was 1.8 yrs (0.3-8.1 yrs) [19].

Bhandare and his colleagues found that 40(20.3%) exhibited clinical hypothyroidism, and of the 62 patients who underwent thyroid panel testing, 14(22.5%) were diagnosed with subclinical hypothyroidism [26]. However, by performed both univariate and multivariate analysis, Tell et al, concluded in the univariate tools with categorical factors, the information if RT to the neck was given as bilateral or unilateral ($p=0.033$), and if there were a surgical intervention ($p =0.001$), had a statistically significant impact on hypothyroidism [19].

Clinically, RT late effects on thyroid gland appear to depend more on the total dose and volume of radiation and the size of the radiation fraction. Because of the endocrine elements of the thyroid gland are reverting post-mitotic cells and are relatively radiation resistant, and thyroid cells have proliferation cycles shorter than those of the endocrine cells. Therefore, damage to the endothelial cells of the thyroid capillary network may be an important mechanism in both early and delayed radiation injury [46, 47].

Recently, Danish Head and Neck Cancer Study Group (DAHANCA)-2013 guidelines for IMRT for head and neck cancers suggests giving an optional constraint of the mean dose to the thyroid gland to <40 Gy wherever feasible [48].

El-Shebiney et al, [23] concluded hypothyroidism is considered a relatively common late RT side effect for HNSCC, as a result, the regular post treatment assessment of thyroid functions are recommended. In addition, they reported that the V30 may predict risk of developing hypothyroidism postRT and suggested that V30 of 42.1%, defined as dose-volumetric threshold of radiation-induced hypothyroidism which can be useful in treatment planning for HNSCC patients.

Several studies in Iraq deal with different agents that causes different levels of hypothyroidism [49-54], nor of them described the effect of radiotherapy on thyroid gland.

CONCLUSION

Old age group, male, co-morbidity and larynx tumors are mostly have hypothyroidism postRT. RT doses more than 66 Gy is highly associated with the incidence of hypothyroidism. fT3 and fT4 has be dropping postRT to HNC whereas TSH is raising. In dosimetry, the mean total dose received by thyroid gland is 4170.13±983.38 cG. The mean 95% dose was 6.8 Gy (median= 4 Gy). The volumes of gland at V40, V50 and V60 are 79.47±28.69 cc, 39.28±19.81 cc, and 38.02±23.83cc, respectively. The incidence of hypothyroidism was (14.3%) and euthyroid incidence rate was (85.7%).

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