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ORIGINAL ARTICLE

Radiotherapy Induced Thyroid Gland Dysfunction among Patients with Head and Neck Cancers

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ABSTRACT

Background: During the planning of 3D conformal radiotherapy for head and neck tumors, it is crucial to prioritize the dosage that reaches sensitive organs such as the thyroid gland. This is because there is a significant likelihood of developing thyroid dysfunction after radiotherapy, which can greatly impact the patient's quality of life.So, we aimed to evaluate thyroid gland function in H&N cancer patients after head and neck radiotherapy to correlate the relation between the RT dose and thyroid gland dysfunctions.

Methods: This prospective study was conducted in Clinical Oncology and Nuclear Medicine Department in Zagazig University Hospitals on 30 patients with head and neck carcinoma who presented to Clinical Oncology department to receive either definitive or adjuvant conformal three dimensional radiotherapy with or without concurrent chemotherapy.

Results: At 6 months of follow up, 73.3% had normal thyroid function while 26.7% had subclinical hypothyroidism and none had overt clinical hypothyroidism. However, at 12 months the rates of normal thyroid function dropped to 50% while subclinical hypothyroidism remained stable at 23.3% and now 26.7% demonstrated progression to clinical hypothyroidism.

Conclusions: There is a high risk of radiation-induced thyroid dysfunction, particularly clinical hypothyroidism, in head and neck cancer patients receiving radiotherapy.

Keywords: Radiotherapy, Thyroid Gland Dysfunction, Head and Neck Cancers.

INTRODUCTION

HNSCC, or head and neck squamous cell carcinoma, is a group of cancerous tumors that affect various parts of the head and neck, including the nasal cavity, salivary glands, pharynx, hypopharynx, larynx, and oral cavity. It ranks eighth in the world in terms of cancer diagnoses. According to GLOBOCAN estimates, there are around 450,000 fatalities and 890,000 new cases of HNSCC occur annually. About 4.5% of all cancer diagnoses are due to this, and fatalities [1].

About 2.68% of all cancer cases and 2.22% of all cancer-related fatalities in Egypt were caused by head and neck cancer, primarily squamous cell cancer [2].

In developing countries, the prevalence of HNSCC is rising because to the escalating use comprises alcohol, areca nut (betel quid), and tobacco (both chewed and smoked). The simultaneous consumption of alcohol and

tobacco has a synergistic impact, resulting in a 40-fold a higher chance of getting HNSCC, or head and neck squamous cell carcinoma when consumed in large quantities. In affluent countries, Head and neck squamous cell carcinoma (HNSCC) associated with HPV is more common than other cancers caused by tobacco and alcohol. HPV-related HNSCC primarily impacts the oral cavity, but rather the oropharynx, hypopharynx, and larynx. It is associated with a median life that is significantly longer—130 months as opposed to 20 months [1].

Treatment options for malignancies of the head and neck include surgery, radiation therapy (RT), chemotherapy, and different combinations of these. Most patients receive a diagnosis of locoregionally advanced illness, which necessitates a multimodal treatment approach involving surgery along with irradiation or concurrent chemoradiation[3].

The mainstay of treatment for head and neck cancer is radiotherapy. The normal tissue in the neck may be harmed by the radiation that is regularly applied to it during radiotherapy. One common consequence is radiation-induced hypothyroidism. Thyroid injury is caused by radiation by the damaging effects it has on the blood vessels, cells that make up the thyroid tissue, and the body's immune system reactions [4].

Hypothyroidism is the typical clinical outcome of irradiation of the thyroid gland in individuals who have received medicinal dosages in the neck region. This phenomenon can be clinically identified as clinical hypothyroidism, which is defined by low large amounts of thyroid stimulating hormone and free T4 levels (TSH). Alternatively, it can be classified as subclinical hypothyroidism, also known as biochemical hypothyroidism, which is characterized by elevated TSH and normal free T4 levels.Subclinical thyroid dysfunction is typically identified through thyroid function tests, however it is often overlooked due to the lack of routine monitoring of thyroid hormone levels throughout follow-up. [5].

The majority of literature discusses the negative outcomes associated with subclinical hypothyroidism, such as impaired heart function, detrimental effects on the heart including atherosclerotic disease and cardiovascular death, increased levels of total and low density lipoprotein, symptoms affecting the body or brain, and the development of clinical hypothyroidism**.**Clinical hypothyroidism presents with symptoms such as cognitive slowing, depression, persistent fatigue, dry skin, accumulation of fluid around the lungs and heart, reduced movement of the gastrointestinal tract, weight gain, intolerance to cold, heart failure, and increased development of fatty deposits in the arteries. Administration of T4 replacement enhances heart function in individuals diagnosed with subclinical hypothyroidism, as well as alleviating symptoms associated with the clinical form of the condition[6].

Multiple studies have assessed the development of hypothyroidism after a thorough course of treatment for head and neck cancer that included a combination of radiation, and chemotherapy. The prevalence evidence exists for radiation-induced

hypothyroidism in head and neck cancer patients to range from 23% to 53%, but in healthy individuals, it is only 3% to 8%. The introduction of innovative radiotherapy (RT) techniques has brought the advantage of increasing the radiation dose to target areas while protecting normal organs such as the heart, lungs, and thyroidresulting in a decrease in the occurrence of late adverse effects from radiation therapy and a rise in patients' quality of life [7, 8].

METHODS

The Zagazig University Hospitals' Clinical Oncology and Nuclear Medicine Department conducted this investigation from May 2022 to December 2023. Approval was obtained from the ethical committee (IRB number 9564-19-6-2022), and ethical agreement was obtained from the patients participating in the study.

Patients were administered either definitive or adjuvant conformal three-dimensional radiation, with or without concurrent chemotherapy.Inclusion criteria included histopathologically-proven head and neck malignancies, age: 18 – 80 years old, normal hematological, kidney and liver functions tests, normal thyroid function tests.The patientswere underwent. External Beam radiation therapy (RT) directed at the thyroid gland and other areas of the head and neck. According to the Eastern Cooperative Oncology Group (ECOG) performance status scale, the patient's score is equal to or lower than 2. [9].

Exclusion criteria included patients with thyroid surgery or thyroid disease who underwent thyroid surgery, thyroid cancer or isotope treatment, patients who received previous head and neck radiotheraby and serious medical comorbidities or other contraindications to radiotherapy or chemotherapy.

All cases had comprehensive evaluations, which included acquiring a comprehensive medical history, carrying out in-depth clinical assessments, executing general and local examinations, conducting dental examinations, and conducting radiographic studies C.T of head and neck, neck ultrasound, chest x ray and pelvi-abdominal ultrasound. The laboratory tests conducted included measurements of TSH, T3, and T4 (before, 6 months & 12 months after radiotherapy). Perform a comprehensive blood analysis, evaluate liver, and kidney function tests.

Treatment protocol:

Thirty patients in all participated in this prospective trial. The radiation therapy (RT) procedure began with computed tomography (CT) simulation, which covered the area from the top of the head to the middle of the chest using slices that were 2-5 mm thick. Participants were rendered immobile by employing a thermoplastic mask, and all CT scans were aligned with the contouring method.

Three-dimensional conformal radiation therapy was administered to each patient (3DCRT) to the head and neck using linear Accelerator (ElektaPresice, serial no.151204), using energy 6 MeV. The GTV, CTV, and PTV, as well as the OARs, were delineated based on the primary head and neck malignancies.

The dose-volume histograms (DVHs), which show the percentage of thyroid gland volume receiving ≥ 10 Gy, ≥20 Gy, ≥V60, and V70, were used to determine V10, V20, V30, V40, V50, V60, and V70 30 Gy≥40Gy, ≥50 Gy ,≥60Gy/&70Gy respectively**.**

The thyroid gland's absolute volume (measured in cm^3) that was not exposed to radiation doses was also recorded at doses of 45, 50, and 60 Gy (also known as VS45Gy, VS50Gy, and VS60Gy (cm^3), respectively.

The main tumor and its surrounding margin were covered by the therapy portals as well as the entire neck region. Following the administration of a radiation dose of 4500 cGy, protective measures were taken to insulate the chord of the spine. The field was expanded to 6000 cGy in total dosage and then a boost was administered exclusively to the primary tumor, reaching a dose of 6600-7000 cGy.

Dosimetric analysis:

For each H&N radiation therapy technique, the contoured target volumes, the following Dosimetric measures were documented for each approach, including the average dosage, maximum dose, and the proportion obtaining a dose ranging from 95% to 105% of the suggested dosage for the planning target volume (PTV). During the process of identifying the risk organs, it is important to include both parotid glands, TMJs, Mandible, Brain stem, Spinal cord, eosophagus, both cochlea and thyroid gland (which is the organ of interest in our study).

The study assessed several dosimetric, including the mean dosage and maximum dose. For all the risk organs, and this dosemetricmeasures were evaluated for thyroid gland to discover the extent of the radiation effect on it, through translating the relation between the volume of thyroid and the dose it received.

Radiotherapy doses:

Phase I encompasses the main location and every level of the neck nodes. The course of treatment include getting 60 Gy in total dose using conventional fractionation, with each fraction delivering 1.8-2 Gy per five days a week. To safeguard the spinal cord, the field was covered after the dosage reached 45 Gy.

Phase II encompasses the main location of the tumor and any positive neck nodes. A boost dosage of 6-10 Gy is administered using traditional fractionation, which involves delivering every fraction, 1.8–2 Gy, once day, for a total of 5 fractions per week. Alternatively, the boost dose can be delivered in 3-5 fractions.

Follow up:

Standardized follow-up encompasses a predetermined schedule of post-treatment control for 5 years. This includes 4 visits or every three months during the initial year. There are two visits in the second year, which happen once every six months. Visits take place every eight to twelve months in the third and fifth years.

Each follow-up included a detailed history with neck examination including primary site, neck nodes and thyroid gland, FT3 (free triiodothyronine), FT4 (free thyroxin), TSH were performed, and Neck U/S was performed for all the patients regardless of clinical symptoms.

Serum Thyroid function test was composed of TSH, FT3, and FT4.

Follow up visits is predetermined schedule of one visit every three months during the initial year. There are two visits in the second year, which happen once every six months. Visits take place every eight to twelve months in the third to fifth years.

TSH 0.270–4.200 μIU/mL, FT3 2.04–4.40 pg/mL, and FT4 0.93–1.71 ng/mL was found.

A baseline TSH, free T3, free T4, were performed before the start of RT then repeated at 6, 12 months following the completion of RT.

A thyroid ultrasonographic examination was conducted for all participants who took part in the study which performed before the start of RT and after completion of the treatment. Ultrasonography The thyroid parenchymal echo structure, thyroid volume, and existence of thyroid nodules were assessed.

Statistical Analysis:

IBM Corp. of Armonk, New York developed the IBM SPSS software package version 20.0, which was used to input and evaluate the data. The tests employed were the Marginal Homogeneity Test, ANOVA with repeated measurements, and the Friedman test.

RESULTS

Thirty patients were included in our study who were proved pathologicaly to have HNC, median age was 58 ranged from (46 to 66 years), 73.3% of patients were males, and 9 of them are current smokers while 6 were ex-smokers. The clinical presentation of these malignancies varies according to anatomical location of the tumor. Among the studied cases according to tumor site there were 11 at oral cavity, 4 at nasopharynx, 2 at hypopharynx, 8 at larynx, 1 at para nasal sinus,and 4 at salivary glands , the table outlines also tumor extention which varies according to anatomical distribution and among pathology the majority of the cases were SCC. Regardingthe stage grouping there were 12 cases were stage I& II, 8 were stage III, 5 were stage IVA and 5 were stage IVB (Table 1).

Among the studied cases there were 12 who had radical operation,and 5 with negative surgical margin (Table 2).

Among the studied cases,the course of treatment was:12 patients had definitive RT while 18 patients were operated before RT. Most of patients were treated with a total dose of 60 Gy in12 patients, 60 -66Gy in 11 patients, and 66-70 Gy in 7 patients. Among the studied cases according to thyroid gland volume there were 5 less than 8 cc and 25 more than 8 cc, with mean 11.52 (±5.91 SD) and range (4.1-36.4) cc (Table 3).

Among the studied cases, there were 2 cases (40%) who developed hypothyroidism among the low volume thyroid group, while there were 6 cases (24%) who developed hypothyroidism among high volume thyroid group (Table 4).

There was significant difference between euthyroid and hypothyroidism group regarding thyroid dose that was higher in hypothyroidism group than euthyroid group (Table 5).

Regardingthe thyroid dose, it ranges between 6.4 and 72.92 and the mean was 47.19 ± 14.05.Thyroid V (%) mean was ranges from 90.24 ± 25.26 to 0.96 ± 4.97 For V10(%) and

V70 (%) while Thyroid VS () mean ranges from 11.79 ± 7.76 to 0.20 ± 0.94 for VS10 and VS70 respectively (Table 6).

A significant statistical difference existed between TSH at baseline, 6 and 12 months and statistically significant difference between T4 at baseline, 6 and 12 months (Table 7).

Regarding thyroid function, there was a substantial statistical difference between the study periods at six and twelve months(Table 8).

***Reagent Preparation*:**Before use, all reagents were brought to room temperature. To make 500 mL of wash buffer, 480 mL of distilled water and 20 mL of wash buffer concentrate were combined.The standards included in the kit vary based on the chosen analytes. Every Standard Cocktail is a 10X concentrate after reconstitution. Standard was prepared using polypropylene tubes by mixing 100 µL of each standard cocktail with calibrator diluent RD6-52. The standard tube held a final volume of 1000 µL. Before making dilutions, the standard was left to sit with mild agitation for at least fifteen minutes. Calibrator diluent RD6-52 was used as the blank, while standard was used as the high standard. Five test tubes with the labels 2–6 was serial pipetted with 100 µL of calibrator diluent RD6–52.

Diluted microparticle cocktail preparation: Before the cap was removed, the vial containing the microparticle cocktail was centrifuged at 1000 x g for 30 seconds. To resuspend the microparticles, the vial was gently vortexed, being careful not to invert it. Diluent RD2-1 was used in the supplied mixing bottle to dilute the microparticle cocktail.

***Diluted biotin-antibody cocktail preparation*:**Before taking off the cap, the vial containing the biotin-antibody cocktail was centrifuged at 1000 x g for 30 seconds. The vial was carefully swirled, being careful not to turn it inside out. In Diluent RD2-1, the biotin-antibody cocktail was diluted.

***Streptavidin-PE preparation*:**During handling and storage, the streptavidin-PE was shielded from light using an aluminum foil-wrapped polypropylene test tube. Before taking off the cap, the streptavidin-PE vial was centrifuged for 30 seconds at 1000 x g. The vial was carefully swirled, being careful not to turn it inside out. In wash buffer, the streptavidin-PE concentrate was diluted. Streptavidin-PE and microparticles were constantly shielded from light.

Steps: Every reagent was ready per the directions. Each well received 50 µl of either the standard or the sample. Each well received 50 µl of a diluted microparticle cocktail. After that, the mixture was shaken at 800 rpm for two hours at room temperature (RT). Washing was done three times: once with the liquid removed from each well, once with 100 µl of Wash Buffer, and once again with the liquid removed. Each well received 50 µl of diluted Biotin-Antibody Cocktail, which was placed on a shaker set to 800 rpm, covered, and allowed to incubate for one hour at room temperature. The steps of wash procedure were repeated. Each well received 50 µl of diluted streptavidin-PE, which was added, and the wells were shaken at 800 rpm for 30 minutes at room temperature. The steps

of wash procedure were repeated. Each well received 100 µl of wash buffer, and the wells were shaken at 800 rpm for two minutes at room temperature. Using a Luminex, it finished reading in ninety minutes. Using standard the calibration curve was made and used for calculating the level of suPAR. The suPAR concentrations were given in ng/mL.

STATISTICAL ANALYSIS

Statistical analysis was performed using the statistical program for social sciences (SPSS) version 28 (IBM Co., Armonk, NY, USA). The Kolmogorov-Smirnov tests were used to validate assumptions for parametric tests. The quantitative data were given as mean and standard deviation (SD) and evaluated using the unpaired student t-test. Categorical data were given as frequency and percentage, then evaluated using the Chi-square test or Fisher's exact test as applicable. Pearson's correlation coefficient was used to determine the level of correlation between two quantitative variables. The diagnostic performance was evaluated using ROC curve analysis with area under the curve (AUC), and a cutoff point was chosen based on the Youden index. Linear stepwise regression analysis was used to determine the associated independent factors for the dependent factor and to predict the value of one variable based on the value of another. A two-tailed P value of <0.05 was judged statistically significant.

RESULTS

As shown in **Table1**, CI-AKI cases were significantly older than the controls (P<0.001). Regarding risk factors, the prevalence of DM and HTN was significantly higher among cases than controls (P<0.001, 0.005, respectively). On the other hand, the CI-AKI group included a significantly lower percentage of smokers than the control group (P=0.007). Moreover, both groups were comparable in terms of sex distribution and the prevalence of hyperlipidemia.

In terms of routine laboratory investigations (**Table 1**), hemoglobin and platelet count were significantly lower in CI-AKI cases than the controls (P<0.001, 0.015, respectively). We also found that creatinine levels (either before or after contrast) were significantly higher in cases than controls (P<0.001). As for uACR, it was significantly increased in cases compared to controls (P<0.001). Noteworthy, no statistically significant difference was detected between both groups regarding total leukocytic count level.

CI-AKI cases elicited significantly higher levels of suPAR marker in comparison to the controls (with a mean of 3.91 ± 0.77 vs. 2.13 ± 0.31 ng/mL, respectively, P<0.001) (Figure 1).

Based on the results of ROC curve analysis, creatinine was a significant predictor of CI-AKI among PCI patients (AUC=0.892, P<0.001). The creatinine cutoff point (>0.89 mg/dL) showed a sensitivity of 85%, a specificity of 75%, positive predictive value (PPV) of 77.3% and negative predictive value (NPV) of 83.3% for the diagnosis of CI-AKI (**Table 2, Figure 2A).** Based on the results of ROC curve analysis, the suPAR marker was a significant predictor of CI-AKI among PCI patients (AUC=0.982, P<0.001). The suPAR cutoff point (>2.55 ng/mL) showed a sensitivity of 92.5%, a specificity of 97.5%, PPV of 97.4% and NPV of 92.9% for the

diagnosis of CI-AKI (**Table 2, Figure 2B)**. Based on the results of ROC curve analysis, combined creatinine marker before contrast and suPAR were significant predictors of CI-AKI among PCI patients (AUC=0.999, P<0.001). Combined creatinine before contrast and suPAR showed a sensitivity of 95%, a specificity of 100%, PPV of 100% and NPV of 95.2% for the diagnosis of CI-AKI (**Table 2, Figure 2C).**

In CI-AKI patients, there was a significant positive correlation between suPAR marker levels and each creatinine level after contrast (r=0.375, P=0.017) and uACR (r=0.396, P=0.011). On the other hand, a significant negative correlation was detected between suPAR marker levels and TLC (r=-0.523, P=0.001), hemoglobin (r=-0.364, P=0.021) and platelet (r=-0.331, P=0.037). Moreover, there was no statistically significant correlation between suPAR levels and age, creatinine level before contrast, or the amount of contrast **(Table 3)**.

In simple regression analysis (**Table 4**), we found that increased levels of creatinine before contrast, uACR, and suPAR were significantly associated with higher odds of having CI-AKI, with coefficients (95% CI) of 21884.22 , 1.57 and 2334.63 and P values of <0.001, 0.018, and 0.005, respectively.

1.

Table1: Distribution of the studied cases according to baseline data (n=30)

Patient Characteristics	**No.**	**%**
Sex		
Male	22	73.3
Female	8	26.7
Age group		
≤50 years	8	26.7
>50 years	22	73.3
Age (years) Min. – Max.	46.0 – 66.0	
Mean ± SD.	54.97 ± 16.17	
Median (IQR)	58.50 (46.0 – 66.0)	
Smoking		
Non-smoker	15	50.0
Ex-smoker	6	20.0
Current smoker	9	30.0
Clinical presentation		
Face/Neck Swelling	17	56.7
Ulcer	12	40.0
Hoarseness of voice	7	23.3
Weakness of mastication Ms	5	16.7
Truisms	1	3.3

Patient Characteristics	No.	%
Dysphagia	14	46.7
Odynophagia	4	13.3
Loss of taste	6	20.0
Clinical presentation		
Headache	1	3.3
Facial pain	1	3.3
Hypo/hyperesthesia in face	1	3.3
Throat pain	3	10.0
Pain in occipital region	1	3.3
Nasal twang of speech	4	13.3
Nasal bleeding	2	6.7
Nasal discharge	1	3.3
Nasal obstruction	1	3.3
Ear pain	2	6.7
Otophonia	2	6.7
Tinnitus	2	6.7
Dry eye	1	3.3
Ptosis	1	3.3
Tumor characteristics		
Tumor Site		
Oral cavity	11	36.7
Nasopharynx	4	13.3
Hypopharynx	2	6.7
Larynx	8	26.7
Para nasal sinus	1	3.3
Salivary glands	4	13.3
Tumor extention		
Para pharyngeal extension	4	13.3
Bone/cartilage invasion	5	16.7
Skull base invasion	1	3.3
Clive's invasion	1	3.3
Pterygoid muscle invasion	2	6.7
Masticator space invasion	3	10.0
Pathology		
Squamous cell carcinoma	20	66.7
Adenoid cystic carcinoma	2	6.7
Mucoepidermoid carcinoma	4	13.3
Adenocarcinoma	4	13.3
Stage Grouping(AJCC staging)		
Early stage		
Stage I	4	13.3

Patient Characteristics	No.	%
Stage II **Locally advanced**	8	26.6
Stage III	8	26.6
Stage IVA	5	16.7
Stage IVB	5	16.7
Treatment modalities		
Radical Surgery+ PORT	12	40
Definitive radiotherapy without surgery	18	60

IQR: **Inter quartile range** SD: **Standard deviation**

Table 2: Distribution of the studied cases according to surgical treatment

	No.	%
Radical operation	12	40
Surgical Margin		
Negative	5	41.7
Positive	7	58.3

Table 3: Distribution of the studied cases according to chemotheraby protocols, radiotherapy sitting, RT dose (Gy), response to treatment and thyroid gland volume (n = 30)

	No.	%
Radiotherapy sitting		
Adjuvant	12	40.0
Definitive	18	60.0
RT dose (Gy)		
60 Gy	12	40.0
60 -66 Gy	11	36.77
66 – 70 Gy	7	23.33
Thyroid gland volume (cm^3)		
≤8	5	16.7
>8	25	83.3
Min. – Max.	4.10 – 36.40	
Mean ± SD.	11.52 ± 5.91	
Median (IQR)	10.92 (8.20 – 12.70)	

IQR: **Inter quartile range** SD: **Standard deviation**

Table 4: Relation between Thyroid volume and incidence of hypothyroidism (n=30)

	Thyroid volume ≤8	Thyroid volume >8
Hypothyroid	2	6
Euthyroid	3	19

Table 5: Relation between Thyroid Mean dose and incidence of hypothyroidism (n=30)

	Euthyroid (*n* = 22)	**Hypothyroidism (*n* = 8)**	***P*-value**
Thyroid dose Mean±SD	46.7±4.9	59.2±3.2	0.001

Statistically significant at $p \leq 0.05$

Table6 : Descriptive analysis of the studied cases according thyroid parameters (n = 30)

Thyroid parameters	**Min. – Max.**	**Mean ± SD.**	**Median (IQR)**
Thyroid D (Gy)			
Mean	8.13 – 67.02	47.19 ± 14.05	50.66 (56.02 – 63.20)
Max	29.90 – 72.92	58.47 ± 9.06	61.45 (56.02 – 63.20)
Min	6.40 – 58.94	33.21 ± 14.92	37.22 (18.90 – 43.60)
Thyroid D (Gy)			
D50	8.70 – 67.74	49.62 ± 12.74	52.81 (46.0 – 58.90)
D100	6.40 – 58.94	33.19 ± 14.91	37.22 (18.90 – 43.60)
Thyroid V (%)			
V10 (%)	10.0 – 100.0	90.24 ± 25.26	100.0 (100.0 – 100.0)
V 20 (%)	8.10 – 100.0	89.62 ± 25.17	100.0 (99.0 – 100.0)
V 30 (%)	0.0 – 100.0	84.97 ± 31.10	100.0 (93.0 – 100.0)
V 40 (%)	0.0 – 100.0	79.70 ± 31.29	95.0 (81.0 – 100.0)
V 50 (%)	0.0 – 100.0	59.33 ± 33.64	63.50 (40.60 – 93.0)
V 60 (%)	0.0 – 99.0	21.12 ± 31.39	4.10 (0.0 – 32.0)
V 70 (%)	0.0 – 27.20	0.96 ± 4.97	0.0 (0.0 – 0.0)
Thyroid VS ()			
VS10	0.20 – 36.0	11.79 ± 7.76	11.20 (8.10 – 12.72)
VS20	0.70 – 36.0	11.57 ± 7.70	10.45 (6.80 – 12.40)
VS30	0.0 – 33.90	10.74 ± 7.67	10.30 (5.20 –12.40)

Thyroid parameters	Min. – Max.	Mean ± SD.	Median (IQR)
VS40	0.0 – 30.0	9.39 ± 7.23	9.20 (4.40 – 11.80)
VS50	0.0 – 99.40	10.01 ± 17.89	6.30 (2.08 – 10.0)
VS60	0.0 – 54.0	3.86 ± 10.30	0.55 (0.0 – 2.70)
VS70	0.0 – 5.10	0.20 ± 0.94	0.0 (0.0 – 0.0)

IQR: **Inter quartile range** SD: **Standard deviation**

Table 7: Descriptive analysis of the studied cases according to thyroid function (n = 30)

Thyroid function	Baseline	After 6 months	After 12 months	Test of sig.	P
TSH					
Min. – Max.	0.60 – 4.10	0.70 – 7.0	0.70 – 13.0	Fr= 19.644*	<0.001*
Mean ± SD.	1.90 ± 0.81	3.05 ± 1.67	5.67 ± 4.39		
Median (IQR)	1.70 (1.30 –2.40)	2.85 (1.80 – 4.0)	3.70(2.10–10.50)		
Sig. bet. Periods	p_1=0.045*,p_2<0.001*,p_3=0.017*				
T3					
Min. – Max.	1.0 – 2.60	0.90 – 2.50	0.60 – 3.0	F= 6.001*	0.116
Mean ± SD.	2.03 ± 0.39	1.85 ± 0.39	1.70 ± 0.65		
Median (IQR)	2.0 (1.80 – 2.40)	1.90 (1.60 –2.10)	1.60 (1.10 –2.10)		
Sig. bet. Periods	p_1=0.051,p_2=0.048*,p_3=0.152				
T4					
Min. – Max.	0.70 – 1.70	0.65 – 1.52	0.50 – 1.1	F= 9.452*	0.021*
Mean ± SD.	1.18 ± 2.5	1.03 ± 2.60	1.03 ± 2.70		
Median (IQR)	1.12(0.99–1.36)	1.01(8.0–1.20)	0.97(0.60–1.30)		

IQR: **Inter quartile range** SD: **Standard deviation**

F: F test (ANOVA) with repeated measures, Sig. bet. Periods was done using **Post Hoc Test (adjusted Bonferroni)**

Fr: **Friedman test**, Sig. bet. Periods was done using **Post Hoc Test (Dunn's)**

p: p value for comparing between **the three studied periods**

p_1: p value for comparing between **baseline** and **after 6 months**

p_2: p value for comparing between **baseline** and **after 12 months**

p_3: p value for comparing between **after 6 months** and **after 12 months**

*: Statistically significant at $p \leq 0.05$

Table 8: Comparison between the two studied periods according to thyroid function (n = 30)

Thyroid function	6 months		12 months		MH	P
	No.	%	No.	%		
Euthyroid	22	73.3	15	50.0	14.500*	<0.001*
Subclinical hypothyroidism	8	26.7	7	23.3		
Clinical hypothyroidism	0	0.0	8	26.7		

MH: Marginal Homogeneity Test

p: p value for comparing between **the two periods**

*: Statistically significant at $p \leq 0.05$

DISCUSSION

The objective the effect of radiation on thyroid function in individuals with head and neck cancer was evaluated in this study This was done by investigating the correlation between the dosage of radiation received by the hypothyroidism that arises and the thyroid gland.

In our study, among the studied cases there were 22 (73.3%) males and 8 (26.7%) females.

This is in agreement with Durrani et al.[10], in their study 48.33% had HNC, among Which males were more frequently afflicted in comparison to females (63.8% vs 36.2%).

Other studies have reported similar findings, showing a higher prevalence of male patients with HNC compared to females [11].

This is also in agreement with Gebril et al.[12],the study found that The risk of developing HNCs was higher in men than in women. This is explained by the fact that, in their study, the incidence of tobacco use was six times higher in men than in women females.

The age range of patients included in our study was between 46 and 66 years, with a total of 8 participants (26.7%) with age less than 50 years and 22 (73.3%) more than 50 years with mean age 54.97 (±16.17 SD).

This result is in agreement with Ruback et al.[13]who evaluated the epidemiological and clinical aspects of a head and neck surgery department and found that the age range of the patients is slightly higher, with a mean age of 60.48 years.

While older persons are more likely to have head and neck cancer, there has been a noticeable rise in instances among young people, particularly for oral cavity and oropharynx cancer, which is linked to HPV 16 infection [14].

In our study, 15 (50%) of the cases we examined were non- smokers, 6 (20%) ex-smokers and 9 (30%) currently smokers.

A study carried out in Saudi Arabia's Riyadh found that 58% of HNC patients were tobacco smokers, resulting in a higher occurrence of oral cancer [15].

Kuhlinet al.[16]revealed that the patients' cigarette use was prevalent tested was 75.15%, while the prevalence of alcohol consumption was 58.25%. The co-occurrence rate of both tobacco and alcohol consumption was 54.00%.

There is strong evidence indicating a clear link between the usage between tobacco and alcohol use with the emergence of head and neck cancer, as demonstrated by multiple researches[17, 18].

A correlation has been documented between being exposed to secondhand smoke for more than 15 years and the occurrence of head and neck cancer, regardless of alcohol consumption [19].

In our investigation, 11 instances (36.7%) were identified at the oral location cavity, 4 (13.3%) at nasopharynx, 2 (6.7%) at hypopharynx, 8 (26.7%) at larynx, 1 (3.3%) at paranasal sinusand 4 (16.7%) at salivary glands.

Countries and regions differ in the prevalence of HNCs, the highest incidences of HNC in the world are found in South Asia, and parts of central and southern Europe[20].In the Middle East, including Egypt, there has yet to be much research that shows the extent or etiology of HNC. Prior hospital-based research in Egypt revealed that HNC accounts for between 17 and 20 percent of all cancers [21].Gebril et al. [12]revealed nasopharyngeal cancer to be the most prevalent form of Head and neck cancer (HNC), closely followed by malignancies of the hypopharynx and oral

cavity.

Durrani et al. [10] reported that the most common site of head and neck cancer (HNC) is the oral cavity, involving 25.9% of patients. This high prevalence may be attributed to the significant consumption of tobacco. Their study found a prevalence of 23.8% for nasopharyngeal cancer, which was greater than the frequency of additional head and neck cancer subtypes. This increase can be attributed to increased exposure to risk factors that are linked to it, like alcohol consumption, tobacco use, and preserved food intake, exposure to certain medications, and a family history of NPC and EBV infection.

In our study, among the studied cases there were 20 (66.7%) with squamous cell carcinoma (SCC), 2 (6.7%) with adenoid cystic carcinoma, 4 (13.3%) with mucoepidermiod carcinoma, 4 (13.3%) with adenocarcinoma.

This agrees with Gebril et al.[12]. The individual who disclosed the information stated the majority of cancers in the head and neck (HNCs) in central Sudan originated from epithelial cells, specifically Squamous Cell Carcinoma (SCC) (98.8 %).

In concordance, Durrani et al.[10]further revealed over 78.1% of HNSCC cases.

In our study according to pathological AJCC stage there were 4 (13.3%) stage I, 8 (26.6%) mentioned findings are consistent with stage II, 8 (26.6%) stage III, 5 (16.7%) stage IVA, and 5 (16.7%) stage IVBGebril et al.[12]Most of the patients had either metastasized (stage IV) or locally progressed malignancies (stage III).

Also, Durrani et al.[10]revealed that TNM stages III (15.1%) and IV (64.6%) accounted for the bulk of HNC patients. Furthermore, 79.7% of the patients had advanced stage head and neck cancer (HNC), which may have been brought on by a lack of hospital resources and a poor level of sickness awareness.

The same results are obtained by Farrag et al.,[15]who found that the majority of cases of HNC (66.6%) in Saudi Arabia are recorded in advanced stages (Stages III and IV), according to a source.

In our study, among the studied cases according to thyroid gland volume there were 5 (16.7%) less than 8 cc and 25 (83.3%) more than 8 cc, with mean 11.52 (±5.91 SD) and range (4.1-36.4) cc, also our study revealed that incidence of hypothyroidism is higher among low volume group (2 cases out of 5) with percentage of 40%,meanwhile the percentage of hypothyroidism in high volume group was 24% (6 cases out of 25).

Those previous results came in line with several investigations have established a definitive correlation between radiation-induced hypothyroidism (RIHT) and thyroid volume. With a decrease in thyroid volume, RIHT is more common. Diaz et al.[22]observed revealed for every unit increase in thyroid volume, the incidence of RIHT dropped by a factor of 0.93, with a 95% confidence interval spanning from 0.88 to 0.98.

Our results also supported by a retrospective study that was conducted on 206 patients who underwent radiation treatment for nasopharyngeal cancer. According to the study, there was an independent risk for thyroid volume of 12.82 or less factor for radiation-induced hypothyroidism (RIHT). When the thyroid volume was 12.82 or less, the incidence of hypothyroidism was 75%. On the other hand, when the volume exceeded 12.82, the incidence of hypothyroidism was 37.31% [6].

On the other hand,Wang et al.[23]The study

discovered that a thyroid volume of 10.6 or less was identified as an independent risk factor with a statistically significant correlation (P=0.000; 72.5% vs. 14.8%) for the development of RIHT. However, same study also found that when patients' thyroid volume was measured, there was no significant correlation with RIHT with a thyroid volume of 10.6 or less were eliminated (P = 0.304). Therefore, the size of the thyroid gland may complicate the analysis of risk factors for recurrent idiopathic hypothyroidism. The study demonstrated that a Dmean value more than 47.3 Gy was a significant predictor of RIHT, with a higher incidence rate of 96.3% compared to 23.1%. This association may be explained by the exclusion of those with a thyroid volume that is 10.6 or less. In concordance with our results,Chyan et al.[24]indicated that the size of the thyroid gland may affect the maximum dosage that can be administered. In patients with a thyroid volume greater than 8, administering a thyroid dose of VS45 ≥3 potentially lessen the likelihood of RIHT. Additional limits are required if the thyroid volume is less than 8, especially with Dmean < 49 Gy, V_{50} < 45%, $VS_{45\geq}$ 3 and $VS_{50\geq}$3.

In our study**,** for the Thyroid D (Gy), the mean values range from 8.13 to 67.02 Gy, with an overall mean of 47.19 ± 14.05 Gy. The median values (with IQR) are slightly lower, ranging from 56.02 to 63.20 Gy. The range of the highest dose (D100) is 6.40 to 58.94 Gy, with a median of 37.22 Gy (IQR 18.90 - 43.60) and a mean of 33.19 ± 14.91 Gy.

Our results showed that most of cases with Dmean>47 Gy were strongly associated with incidence of RIHT with percentage of 75% from all cases who developed hypothyroidism. Similar to our study,Nakhla et al.[25]The study obtained thyroid dosage parameters, including From the dose-volume histogram (DVH) of the treatment planning system, the mean dose (D mean), maximum dosage (D max), minimum dose (D min), and dose of 50% volume (D 50%) are determined.

Chow et al. [26]An analysis of 29 trials, comprising 4,530 individuals with head and neck cancer (HNC) in total found that using VS60 > 10 could be advantageous in reducing the occurrence of radiation-induced hearing loss (RIHT).

In consistent with our results,Xu et al. [27]revealed revealed in the hypothyroidism group as opposed to the normal group, the thyroid dosage parameters Dmean and V50 were noticeably higher. Radiation-induced hypothyroidism with a 3-year cumulative incidence of Dmean< 5160 cGy and Dmean> 5160 cGy was 44.6% and 67.8%, respectively, in the group with Dmean (P = 0.036). V50 was less than 54.5% in the lower incidence group and more than 54.5% in the higher incidence group (29.9% vs. 66.1%, P = 0.025).

Our study's findings showed that the frequency of hypothyroidism in individuals withV50 ≤ 95% and V50 > 95% were 25% and 75% respectively.

However, Chow et al. [26]revealed found patients with V40 ≤ 85% and V40 > 85% had a prevalence of hypothyroidism of 21.4% and 61.4%, respectively. The authors recommended that the standard for the thyroid's dosage volume be should be established as V40 ≤ 85%. In comparison to other research, this dose restriction is relatively lenient.

Also,Zhai et al. [28]prospectively examined 135 individuals and found that several factors related to the thyroid, including

Hypothyroidism has been linked to Dmin, Dmean, V30, V35, V40, V45, and V50 parameters. Dmean, V45, and V50 in particular were found to be independent predictors. The study found that patients with a Dmean more than 45 Gy had a relative risk of hypothyroidism that was 4.9 times higher than patients who had a lower dose. Based on these findings, According to the authors, the thyroid dosage ought to be adjusted to V45 < 50% and V50 < 35%.

Generally**,** a meta-analysis of five publications on radiation-induced hypothyroidism revealed a correlation between hypothyroidism and various thyroid dose-volume characteristics, including as maximal dosage (Dmax), min, Dmean, and V10-V70. The study, however, was unable to determine the thyroid's ideal dosage threshold[6].

Our study found a substantial and statistically meaningful difference in TSH levels at the beginning of the study (Mean 1.90 ± 0.81) , 6 months (Mean 3.05 ± 1.67)and 12 months (Mean 5.67 ± 4.39) and statistically significant difference between T4 at baseline(Mean 1.18 ± 2.50) , 6 months (Mean 1.03 ± 2.60) and 12 months (Mean 1.3 ± 2.70) .

These findings are somewhat different from other results, where Bernát and Hrušák[29]revealed that there were no differences in hormone levels between the control group and the participants with early follow-up (0–60 months). In contrast to the control group, patients whose follow-up lasted more than 60 months (60+) showed different hormone levels. The reason for this disparity could be the subjects' differences, since the patients in the control group were surgical patients with less advanced disease. However, when compared to our findings, their data show that the three factors (TSH, FT3, and FT4) had a negligible difference. Radiation has the ability to change these parameters, but not right away after exposure, as shown by the examination of the three patient groups before, during, and after radiation therapy.

In contrast to our results,Nakhla et al. [25] indicated that TSH levels exhibited a substantial drop in the groups who received treatment in comparison to the control groups. Nevertheless, there was a substantial rise in FT4 levels, and these alterations did not follow a pattern that depends on dose. The FT3 levels of the treatment groups and the control group did not differ significantly. Following treatment, there was a significant negative association between the patients' TSH level and their thyroid's average D and D50%. On the other hand, there was a positive association seen at the FT4 level. This could be ascribed to variations in the dosing protocol.

Lertbutsayanukul et al.[30]discovered that prior to therapy, a high TSH value (≥ 1.55 μU/ml) increases the likelihood of developing hypothyroidism caused by radiation which is in consistence with our results that show 75% of cases developed RIHT had pre treatment TSH value > 1.55 μU/ml.

Rooney et al.[7]involved 203 individuals diagnosed having cancer of the head and neck, nasopharyngeal carcinoma excluded. The results showed that although the thyroid gland's size was a major factor in predicting hypothyroidism, the initial TSH level before treatment did not have any correlation with the development of hypothyroidism. Nevertheless, a notable association was observed between the initial TSH level and thyroid volume. Specifically, individuals with a lower thyroid volume exhibited higher

pretreatment TSH levels, potentially due to the substantial variation in the number of participants included in our study.

Our study found that after 6 months, 73.3% of participants had normal thyroid function, 26.7% had subclinical hypothyroidism, and none had overt clinical hypothyroidism. Nevertheless, by the time the infants reached 12 months of age, the percentage of individuals with normal thyroid function decreased to 50%. In contrast, the prevalence of subclinical hypothyroidism remained steady at 23.3%, and an additional 26.7% of individuals showed progression to clinical hypothyroidism. The considerable decrease in normal thyroid function and the increase in clinical hypothyroidism after 12 months, as compared to 6 months, is supported by strong statistical evidence, shown by a p-value of less than 0.001.

In agreement with our results,Wang et al.[23]indicated that the prevalence of RIHT was 36.9%. Notably, out of the 6 patients, 3 patients experienced a progressive transition from hyperthyroidism to a normal thyroid function (euthyroid), whereas 1 patient eventually developed hypothyroidism. The shift from hyperthyroidism to hypothyroidism is believed to be due to a temporary thyroid hormone released as a result of significant damage to the thyroid parenchymal cells. One possible explanation for the change from hyperthyroidism to euthyroidismto an augmented permeability of cellular membranes that remained unaltered. These answers provide a clear understanding of the temporary fluctuations in thyroid function observed in the patients in their series.

Comparably**,** a Systematic Review by Rooney et al.[7]found the estimated occurrence of RIHT varied significantly, with a median estimate of 36% (range from 3% to 79%).

Another recent study by Lian et al.[31]found that 132 patients had nasopharyngeal carcinoma (NPC), according to the research. Out of the total number of patients, 56 individuals (42.4%) were diagnosed with hypothyroidism. Among these, 41 patients (73.2%) had subclinical hypothyroidism, while 15 patients (26.8%) had clinical hypothyroidism which is similar to our study.

CONCLUSIONS

Our investigation revealed a significant likelihood of radiation-induced thyroid dysfunction in head and neck cancer patients receiving radiotherapy, more especially clinical hypothyroidism. Over the course of a year, there was a notable rise in the occurrence of clinical hypothyroidism, from 0% to 26.7%. This suggests that there were considerable long-term effects on the thyroid gland. The thyroid doses averaged around 50Gy, indicating that the majority of individuals were exposed to significant levels of radiation. The dosimetry parameters exhibited significant variability, which can be attributed to variations in the administered treatment doses. Based on the established correlation between the amount of radiation received and the resulting damage, we suggest regularly monitoring thyroid function following radiotherapy and customizing treatment plans to reduce needless exposure of the thyroid to radiation.

Recommendations

- Head and neck cancer patients receiving radiotherapy should undergo regular monitoring of thyroid function, particularly in the first year following treatment. This will enable early detection of any abnormalities and facilitate timely intervention to manage hypothyroidism effectively.
- Thyroid gland dosimetry should be considered during treatment planning to

minimize radiation dose to the thyroid, thereby reducing the risk of developing hypothyroidism. Individualized treatment techniques, such as intensity-modulated radiation therapy (IMRT), should be explored to spare the thyroid gland from excessive radiation exposure.

- Patients should be educated about the potential risk of hypothyroidism associated with radiotherapy, its symptoms, and the importance of regular follow-up. Counseling sessions should be conducted to address patient concerns, provide support, and ensure compliance with thyroid function monitoring.
- Further research with larger sample sizes is needed to validate these results.
- Extended follow-up studies are necessary to assess the persistence and late-onset of hypothyroidism in head and neck cancer survivors.
- Future studies should include a control group to better understand the specific impact of radiotherapy on thyroid function.

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Competing interests

The authors declare that they have no competing interest.

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