Factors Affecting Thyroid Dysfunction in Patients with Head and Neck Cancer Receiving Chemo-radiation Therapy

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Abstract

Background: Head and neck cancers are considered the 6th most common cancer worldwide. For patients with advanced disease, combined modality treatment including chemo-radiation (CRT) as first-line treatment had improved outcomes for patients with locally advanced disease. The association between radiation exposure and the occurrence of thyroid cancer has been well documented, and the two main risk factors for the development of thyroid cancer are the radiation dose delivered to the thyroid gland and the age at exposure. The risk increases after exposure to a mean dose of more than 0.05-0.1 Gy (50-100 mGy. Nurses' role is not only in the maintenance of the treatment and its adverse effects, but also to act as information disseminators about the disease and its treatment, offering relief measures and helping the patients to cope with the disease **Aim:** Assess factors affecting thyroid dysfunction in patients with head and neck cancer receiving radiation or chemo-radiation therapy. **Design:** A descriptive research design was utilized for this study to meet the aim of the present study. **Setting:** chemotherapy and radiology units of the Main University Hospital and Charity Ayadi Almostakbl center for cancer treatment in Alexandria.. **Subjects:** A convenience sample of 100 adult male and female patients. **Study tools:** Three tools were used. Tool (I) **A** socio-demographic and clinical data interview schedule, Tool (II) Assessment of head and neck cancer patient's knowledge and Tool (III) Assessment of chemo-radiation side effects on thyroid gland structured interview schedule. **Results:** The current study showed that there was statistical significant difference between socio – demographic characteristics and clinical data and patients overall Knowledge score and all over sign and symptoms.. **Conclusion:** The provision of effective education was found to have a profound impact on improving patients' knowledge and practice. **Recommendations:** Regular testing of thyroid function in patients undergoing radiation or chemo radiation can help in diagnosing thyroid dysfunction at the subclinical stage, before it progresses to clinical hypothyroidism. Larger multi-institutional studies with longer follow-up are needed to study the morbidity associated with post radiation thyroid dysfunction further.

Keywords: Thyroid Dysfunction, Head and Neck Cancer, Radiation Therapy, Chemoradiation Therapy.

Introduction:

Head and neck cancers are considered the 6th most common cancer worldwide; more than ninety percent of cancers are SCC that arises from the mucosal cell lining of the oral cavity, larynx, and oropharynx **(El-Shebiney, et al., 2018)**. Approximately 50,000 patients are diagnosed annually with squamous cell carcinoma head and neck in the United States. Worldwide, approximately 600,000 patients are afflicted. Around 57.5% of global head and neck cancers occur in Asia. Around 60% of these patients present with locally advanced nonmetastatic disease **(Immanuel1, et al., 2019).**

Majority of head and neck tumours are locoregionally advanced at the time of diagnosis. Concurrent chemoradiotherapy is the standard of care for these patients. Radiation portals cover the primary tumour along with the whole neck, thereby including the thyroid gland in the radiation field leading to its dysfunction. The incidence of thyroid dysfunction varies from 10-46% and manifests as elevated TSH levels. About 70% of patients receive primary RT and 30% receive surgery with or without postoperative radiation therapy (RT). For the majority of patients with early-stage HNSCC, single modality treatment may be sufficient for cure. For patients with advanced disease, combined modality treatment including chemo-radiation (CRT) as

first-line treatment had improved outcomes for patients with locally advanced disease **(Rønjom, 2016).**

Radiation therapy is often used to treat head and neck cancer (HNC). RT can damage blood vessels that nourish muscles, nerves, and bones resulting in a progressive "radiation fibrosis syndrome", which causes a variety of complications. The likelihood and severity of complications depend on several factors, including the total dose of radiation delivered, over what time it was delivered, and what parts of the head and neck received radiation **(Tolentino, et al., 2011).**

The side effects of RT for HNC are divided into early (acute) and long-term (chronic) effects. Early side effects occur during therapy andimmediate post-therapy period approximately two to three weeks after the completion of a course of RT. Late effects can manifest any time thereafter, from weeks to years later **(Brook. 2020).**

Patients are usually most bothered by the early effects of RT, although these will generally resolve over time. Knowledge of the radiation side effects can allow their early detection and proper management. Late side effects include permanent loss of saliva; osteoradionecrosis; pharyngoesophageal stenosis; dental caries; oral cavity necrosis; fibrosis; radiation recall myositis, impaired wound healing; skin changes and skin cancer; lymphedema; hypothyroidism, hyperparathyroidism, lightheadedness, dizziness and headaches; secondary cancer; and eye, ear, neurological and neck structures damage **(Morgan & Sher, 2020; Stubblefield, 2017).**

However, patients who receive radiotherapy to the neck are at increased risk of developing thyroid dysfunction, as the thyroid gland is highly sensitive to the carcinogenic effects of 3 exposure to ionizing radiation which is usually seen in the form of biochemical hypothyroidism but may also present as clinical hypothyroidism or thyrotoxicosis **(Iglesias et al., 2017).** One-third of thyroid tumors occurring after radiation exposure are malignant, and most radiation induced-thyroid cancers are papillary thyroid carcinoma (PTC). These patients are also more likely to develop both benign and malignant nodules of the thyroid gland. Thyroid dysfunction after radiation is most often manifested by elevated serum concentration of thyroid stimulating hormone (TSH) **(Sachdev, et al., 2017).**

Radiation-induced HT may be either clinically overt, with increased serum thyrotropin (TSH) and low serum-free thyroxine (fT4) concentrations, eventually accompanied by clinical signs such as intolerance to cold, bradycardia, hypotension, fatigability, and slow reflexes or subclinical HT manifested by elevated TSH and normal serum-fT4 concentrations. Radiationinduced HT commonly occurs within five years and its possibility of occurrence may be prolonged from twenty to twenty-five years post head and neck irradiation. The peak incidence of occurrence of radiation-induced HT is at two to three years after RT (Lin, et al., 2018).

The association between radiation exposure and the occurrence of thyroid cancer has been well documented, and the two main risk factors for the development of thyroid cancer are the radiation dose delivered to the thyroid gland and the age at exposure. The risk increases after exposure to a mean dose of more than 0.05-0.1 Gy (50-100 mGy **(Sroussi, et al., 2017).**

Hypothyroidism is a frequent late effect after definitive radio therapy. As the condition has been linked to increased risk of cardiac disease and mortality and decreased quality of life, it is important to consider the risk of radiation-induced hypothyroidism (RIHT) when planning radiation treatment. The size of the thyroid gland and the radiation dose to the gland are key factors in the development of RIHT, and both these factors should be considered when determining dose constraints for the thyroid gland. A risk of RIHT below 25% is recommended. Furthermore, routine assessment of thyroid gland function should be offered after radiotherapy in the neck area **(Rønjom, 2016).**

During radiotherapy, the patient may be affected by feelings of distress and helplessness, in addition to possible aforementioned complications, which is indispensable the role of nurses in performing

nursing consultations, which is based on orientation, prevention, treatment, and rehabilitation throughout the patient's stay in the radiotherapy department thorough education to patients and families, which recognize the competence of the nurse after going through nursing consultation, this becoming a professional reference in the radiotherapy sector **(Primo, et al., 2016)**.

Nurses' role is not only in the maintenance of the treatment and its adverse effects, but also to act as information disseminators about the disease and its treatment, offering relief measures and helping the patients to cope with the disease. Therefore, the challenge of nursing care for this population relates to the different physical and psychosocial demands which need to be attended to through different forms of communication and counseling, besides specialized theoretical and practical knowledge involving care **(Abdel Hady, et al., 2020).**

Aim of the Study

This present study aimed to

- Assess factors affecting thyroid dysfunction in patients with head and neck cancer receiving radiation or chemo-radiation therapy.
- Retrospectively evaluate the early and late changes in the thyroid function in patients with head and neck cancer receiving chemo-radiation therapy.

Research questions of the study:

Q1: What are factors affecting thyroid dysfunction in patients with head and neck cancer receiving radiation or chemo-radiation therapy?

Q2: What are the early and late changes in the thyroid function in patients with head and neck cancer receiving radiation or chemo-radiation therapy?

Materials and Method

Materials Research Design:

A descriptive research design was utilized for this study.

1. **Setting:** This study was conducted at both chemotherapy and radiology units of the Main University Hospital and Charity Ayadi Almostakbl center for cancer treatment in Alexandria.
2. **Subjects:** A convenience sample of 100 adult male and female patients admitted to the abovementioned settings diagnosed with cancer and received chemo-radiation were included in the study.

Epi info 7 will be used to estimate the sample size using the following parameters:

- o Total population size estimated 100 patients
- o Expected frequency: 50%
- o Acceptable error: 5%
- o Confidence coefficient:95%
- o Minimum sample size of 100 patients

Patients were considered eligible to participate in the study if they met the following criteria:

- Adult of both sexes, (18≤60) years old.
- Agreeing to participate in the study.
- Able to communicate freely and effectively.
- Adequate cognitive state i.e. able to understand and collaborate.
- Patient had to have been diagnosed with head and neck cancer (history of thyroidectomy, thyroid neoplasm disease or thyroid disorders
- Patients who receive chemotherapy in combination with radiotherapy (chemo-radiation).

3-**Tools**: Three tools were utilized for the purpose of data collection.

Tool I: A socio-demographic and clinical data interview schedule: It was included two parts:

Part I: Patients' socio-demographic data: this part was included items related to sociodemographic data, such as age, gender, level of education, occupation, marital status, residence, and clinical data as family history, medical history, and surgical history, patient daily habit such as smoking and the medications.

Part II: Clinical data: this part was included past medical history (Comorbidity) past, present and family health history, previous hospitalization, and the length of hospitalization. Surgical diagnosis, Head and neck cancer (Site of tumor), previous

chemo/radiation therapy, mode of treatment, duration of chemo/radiation therapy, chief complain will be obtained from the patient's medical records and interview.

Tool II: Assessment of head and neck cancer patient's knowledge. This tool was developed by the researchers based on reviewing the relevant recent literature **(Rønjom, 2016)** It will include group of structured questions to identify cancer patients knowledge about radiotherapy and chemotherapy .this question will cover the following area: Definition of thyroid gland, function of thyroid gland, thyroid hormones, definition of hypothyroidism, sign and symptoms of hypothyroidism, Line of cancer treatment (surgery, chemotherapy, radiotherapy or combination), types of radiotherapy and chemotherapy, sessions of radiation and chemotherapy, diagnostic procedure and laboratory investigation done to identify thyroid gland changes and for follow-up, iodine status, the total dose of radiation delivered, over what time it was delivered, and what parts of the head and neck received radiation.

Scoring System of Knowledge:

The total score will be ranged from 0-30. Each correct answer responses will be given the score of one and the wrong or I do not know answer will be given the score of zero. The scores of the items will be summed - up and will be converted into percentages. Total nurse's score % = (the observed score / the maximum score) x 100. The patients' knowledge level will be based on Benners' stages (Benner, 2001).That is described as follows:

Total score	Category
≤90 %	Excellent
80 to %89 %	Very good
70 to %79 %	Good
60 to %69 %	Fair
>60 %	Fail

Tool III: Assessment of chemo-radiation side effects on thyroid gland structured interview schedule

This tool will be adopted by the researchers from (Zulewski, et al., 1997) it utilizes 7 symptoms and 6 signs to assess the thyroid status, and diagnose hypothyroidism.

Signs

1. Slowness of movements
2. Observing patient walking and sitting.
3. Ankle reflex observing relaxation.
4. Coarse skin, dermatologist finding on examining skin of the hand, forearm, and elbow for thickness and roughness.
5. Periorbital puffiness.
6. Observing periorbital swelling.
7. Cold skin Comparing temperature of hand with examiners.

Symptoms

1. Diminished sweating: Questioning regarding sweating in normal or warm room.
2. Hoarseness of voice: Questioning regarding change in speaking or singing voice.
3. Paresthesia: Questioning regarding subjective sensations.
4. Dry skin Questioning regarding dryness of skin and requiring treatment inform of moisturizing agent Constipation Questioning regarding bowel habit and use of laxatives.
5. Hearing impairment Questioning regarding difficulty in hearing 6. Weight increase Questioning regarding increase in weight.

Zulewski's Clinical Score and Its Validation in Hypothyroid Patients. The aim of this tool will be used to evaluate the prevalence of various signs and symptoms of hypothyroidism and to correlate with the biochemical investigations and clinical Zulewski's score in hypothyroid patients. Zulewski's scoring on the basis of the presence of various signs and symptoms. Identified on basis of Point given if present.

A score >5 points defined hypothyroidism, while a score of 0-2 points defined euthyroidism. The patient was clinically considered hypothyroid if score was ≥5, euthyroid if score was then correlated.

Method

The study will be accomplished as follows:

- Written approval from the Research Ethics Committee, Faculty of Nursing, Alexandria University will be obtained.
- An official permission from the Faculty of Nursing, Alexandria University will be obtained and will be directed to the responsible authorities of the study settings to take their permission to conduct the study after explaining the aim of the study.
- Written informed consent will be taken from each nurse after explaining the nature and benefits of this research. The researcher emphasized that participation in the study was entirely voluntary and each patient has the right to withdraw from the study at any time without giving any reason. As well, anonymity and confidentiality were assured through coding the data.

Tools development:

- Tool I and II will be developed by the researchers while tool III will be adopted by the researchers.
- All study tools will be tested for content validity by 5 experts in MedicalSurgical Nursing to assure the content validity, clarity of items, comprehensiveness, appropriate, translation and the necessary modifications will be done.
- Reliability of the tools will be tested using an appropriate statistical test.

Pilot study:

- A pilot study will be carried out on 10% of patients fulfilling the inclusion criteria to test the clarity, feasibility, and applicability of the tools. The necessary modifications will be done accordingly. The pilot sample will be excluded from the study subjects.

Data collection:

- Data was collected at the morning shift every day.
- The researchers started by introducing themselves, explaining the purpose of the study.
- The researchers ensured that the place where the interviews were conducted is calm, with adequate lighting, well arranged, and comfortable.
- Tools filling took about 30-45 minutes.
- Each patient will be interviewed individually once by the researcher to collect the needed data related to risk factors of thyroid gland dysfunction of head and neck cancer patients receiving chemo radiation at radiology and chemotherapy units.

Zulewski's clinical score

- A total of 100 patients will be enrolled who met the inclusion criteria which included following: Adult patient of diagnosed hypothyroidism and willing to participate in the study. A repeat thyroid profile was done for all patients after written and informed consent.
- Patients who had deranged thyroid profile parameters and diagnosed with hypothyroidism within past 6 months were included in the study, and detailed clinical history and physical examination were done along with the review of old medical records. The Zulewski's clinical score for hypothyroidism was then calculated.

Ethical Considerations:

- A written patients' informal consent to participate in the study was obtained after explanation of the purpose of the study.
- Anonymity, privacy of the study patients and confidentiality of the collected data were assured throughout the study. Patients also, were informed that their participation was on voluntary base they have the rights to withdraw from the study at any time without any penalty.

Results:

Table (1): Shows the frequency distribution of the study group according to their socio-demographic characteristics. Regarding patient's age, the results revealed that more than half (55 %) of (HNC) patients were aged from 50 or< =60years old. **The vast majority** of them were male, married, and from urban area (85 %, 86%,80%) respectively. **In relation to the educational level**, it was

observed that the highest percentage of (HNC) patients (70%) were illiterate. **In relation to occupation**, it was found that nearly three quarters (67%) of the patients group were not working. **Concerning income**, all of the studied patients in the study group were not have enough income.

Table (2): Shows the frequency distribution of the study group according to patients past medical history and their family history. In relation to the family history, it was noticed that, the around half of (HNC) patients had family history of cancer (46%). It was noticed that (HNC) patients had relative degree (76%) respectively. **In relation to patients medical history**, it was noticed that (40%) of (HNC) patients had hypertension. and the vast majority of them (84%) had previous surgery. **Regarding primary site of tumor** the table shows that more than half of (HNC) patients (54%) had oral cavity cancer. **The table also shows that** all (HNC) patients (100%) had chemo radiation as a line of treatment from months to 1year. Also it was found that, the highest percentage of study group (71%) had thyroid enlargement from 6to more than 12 months from chemo radiation therapy. **Concerning experienced symptoms**, this table revealed that, the study group patients (33%) had swelling of the neck and hoarseness. also all patients had decreased in laboratory investigation concerning thyroid gland,(T3,T4) and increase TSH. **Regarding dose of radiation,** it was noticed that the highest percentage of patients (77%) were>60 Gy.

Table (3): shows the distribution of the head and neck cancer patients **in relation to their smoking and medication habits. Concerning smoking**, this table revealed that, the vast majority of head and neck cancer patients (85%) were smokers. Also it was found that, the highest percentage of them (70%) started smoking in the age group of less than 18 years. **Concerning over the counter medication**, the highest percentage of head and neck cancer patients (85%) took analgesics as an over counter medication.

Table (4) reveals that all patients had fail knowledge related to thyroid gland and symptoms, with Mean ± SD of (**11.90±16.0**). **The table reveals** that all patients(100%) had Hypothyroidism. Regarding Mean ± SD of Zulewski's clinical score for Signs of hypothyroidism were (6.73±2.44),while Mean ± SD of Zulewski's clinical score for Symptoms of hypothyroidism were (**11.90**±0.36). In relation to Mean ± SD of Zulewski's clinical score for Signs and Symptoms of hypothyroidism were (**18.63±2.57**).

It can be observed from table (6) that, there was statistical significant difference between socio – demographic characteristics (Age, Gender, Level of education, Occupation) and patients overall Knowledge score (**4.479* (0.005*), 7.070* (<0.001*), 2.878* (0.027*) , 6.202* (0.003*)) respectively.** It can be also noted that, there was statistical significant difference between socio – demographic characteristics (Age and Occupation) and patients **Overall Signs and symptoms** (**16.816*(<0.001*), 5.980* (0.004*)) respectively.**

It can be observed from table (7) that, there was statistical significant difference between clinical data (**Experienced symptoms**, **Types of family cancer**, **Previous surgery**, **Site of tumor**) and patients overall Knowledge score (**3.086* (0.020*), 3.791* (0.013*), 6.804* (<0.001*),2.811* (0.030*)) respectively.** It can be also noted that, there was statistical significant difference between clinical data (**Past medical history, Age of onset of thyroid enlargement** and **Site of tumor**) and patients **Overall Signs and symptoms** (**7.424* (<0.001*), 8.306* (<0.001*),10.612* (<0.001*)) respectively.**

Table (8) showed that, there was statistical significant difference between clinical data (**Chemo regimen**, **Radiation dose**, and **Follow up**) and patients overall Knowledge score (**3.116* (0.049*),6.680* (0.002*), 4.607* (0.012*)) respectively.**

It can be also noted that, there was statistical significant difference between clinical data (**Time of disease diagnosis, Mode of treatment** ,**Chemo regimen, Radiation dose, and Radiation dose**) and patients **Overall Signs and symptoms** (**7.258* (<0.001*), 2.220* (0.029*), 2.220* (0.029*),12.834* (<0.001*), 5.889* (0.004*), 3.317* (0.040*)) respectively.**

Regarding step1, table (9) indicated that, there was positive statistically significant correlation between patients' age and **overall Signs and symptoms** ($P =<0.001^*$, $R^2= 0.312$) , ($P =<0.001^*$).**Concerning step2**, The table also showed that, there was positive statistically significant correlation between patients' age, Age of onset of thyroid enlargement and **overall Signs and symptoms** ($R^2= 0.439$, $F= 39.707^*$,$p<0.001^*$).**Concerning step3**, The table also showed that, there was positive statistically significant correlation between patients' age, Age of onset of thyroid enlargement, Past medical history and **overall Signs and symptoms** ($R^2= 0.495$, $F= 33.318^*$,$p<0.001^*$).

Part I: Patient's socio-demographic characteristics and clinical data.

Table (1): The frequency distribution of the study group according to their socio demographic characteristics.

Students' sociodemographic characteristics	No	%
Age		
20 < 30	12	12.0
30 < 40	11	11.0
40 < 50	22	22.0
50 ≤ 60	55	55.0
Gender		
Male	85	85.0
Female	15	15.0
Marital status		
Single	1	1.0
Married	86	86.0
Divorced	3	3.0
Widow	10	10.0
Level of education		
Illiterate	70	70.0
Can read and write	16	16.0
Primary	6	6.0
Secondary	7	7.0
University	1	1.0
Residence		
Rural	20	20.0
Urban	80	80.0
Occupation		
Not work	67	67.0
Manual work	18	18.0
Housewife	15	15.0
Income		
Insufficient	100	100.0

Table (2): The frequency distribution of the study group according to patients past medical history and their family history.

Clinical data	No	%
Family past medical history		
Diabetes Mellitus	18	18.0
Hypertension	20	20.0
Cardiovascular disorders	5	5.0
Gastrointestinal disorders	2	2.0
Endocrine disorders (hypo/hyperthyroidism)	9	9.0
Cancer	46	46.0
Types of family cancer		
Non	8	8.0
Colon	31	31.0
Breast	11	11.0
Head and neck	50	50.0
Relative degree		
Non	11	11.0
First degree	76	76.0
Second degree	13	13.0
Past medical history		
Diabetes Mellitus	38	38.0
Hypertension	40	40.0
Cardiovascular disorders	3	3.0
Endocrine disorders	8	8.0
Rheumatoid arthritis	11	11.0
Site of tumor		
Oral cavity	54	54.0
Larynx	20	20.0
Oropharynx	14	14.0
Maxilla	6	6.0
Hypopharynx	6	6.0
Used treatment method		
Radiotherapy and chemotherapy	100	100.0
Age of onset of thyroid enlargement		
3to less than6 months	29	29.0
6 to more than 12 months	71	71.0
Experienced symptoms		
Swelling of the neck	33	33.0
Hoarseness	33	33.0
Difficulty of swallowing	29	29.0
Nervousness and irritability	2	2.0
Palpitation	3	3.0
Duration of chemo-radiation therapy		
Months to 1year	100	100.0
Previous surgery		
Yes	84	84.0
No	16	16.0
Chemo regimen		
Weekly CDDP	69	69.0
3 Weekly CDDP	19	19.0
Weekly Carboplatin	12	12.0
Radiation dose		
<60 Gy	9	9.0
60 Gy	14	14.0
>60 Gy	77	77.0
Follow up		
6 months	91	91.0
9 months	5	5.0
12 months	4	4.0
TSH		
Above normal range	100	100.0
T3		
below normal range	100	100.0
T4		
below normal range	100	100.0

Table (3): The distribution of the head and neck cancer patients in relation to their smoking and medication habits. (n= 100)

	Study (n = 100)	
	No.	**%**
Smoking		
15. Presence of smoking.		
Yes	85	85.0
No	15	15.0
16. Age of starting smoking?		
less than 18 years	70	70.0
18-25 years	15	15.0
Drugs		
21. Over counter medication.		
No	8	8.0
Antihistamines	5	5.0
Analgesics	75	75.0
Opiates	2	2.0
Tricyclic antidepressants	5	5.0
Cortisone	5	5.0

Table (4): Descriptive analysis for knowledge and symptoms scores (n = 100)

	No	**%**
Knowledge		
Fail	100	100.0
Fair	0	0.0
Good	0	0.0
Very good	0	0.0
Excellent	0	0.0
	Mean	**±SD**
Mean percent score of knowledge	**11.90**	**16.0**
Total score of knowledge	**3.57**	**4.89**

Overall Signs and symptoms	**No**	**%**
Euthyroid <3	0	0.0
Intermediate 3 – 5	0	0.0
Hypothyroidism >5	100	100.0
	Mean	**±SD**
Signs	6.73	2.44
Symptoms (Zulewski's clinical score for hypothyroidism)	11.90	0.36
Overall Signs and symptoms	**18.63**	**2.57**

Table (5): Correlation between the study variables (n = 100)

		Overall knowledge	**Signs**	**Symptom's**	**Overall Signs and symptoms**
Overall knowledge	R				
	P				
Signs	R	-0.176			
	P	0.080			
Symptoms	R	-0.196	0.289*		
	P	0.051	0.004*		
Overall Signs and symptoms	R	-0.195	0.991*	0.416*	
	P	0.052	<0.001*	<0.001*	

r: Pearson coefficient *: Statistically significant at $p \leq 0.05$

Table (6): Relation between demographic data and study variables (n= 100)

Students' sociodemographic characteristics	Overall knowledge scale	Overall Signs and symptoms
Age		
20 < 30	8.0±6.18	14.92±2.07
30 < 40	4.27±5.61	17.64±2.50
40 < 50	3.0±3.51	18.82±2.04
50 ≤ 60	2.69±4.48	19.56±2.07
F(p)	**4.479* (0.005*)**	**16.816*(<0.001*)**
Gender		
Male	4.16±5.08	18.51±2.69
Female	0.20±0.41	19.33±1.63
t(p)	**7.070* (<0.001*)**	**1.614 (0.117)**
Marital status		
Single	2.0	21.0
Married	4.09±5.08	18.53±2.69
Divorced	0.67±1.15	21.0±0.0
Widow	0.10±0.32	18.50±1.35
F(p)	**2.503 (0.064)**	**1.190 (0.318)**
Level of education		
Illiterate	1.0	21.0
Can read and write	3.56±5.67	18.06±2.91
Primary	7.33±6.25	21.0±0.0
Secondary	7.86±6.44	18.43±3.55
University	2.86±4.14	18.54±2.42
F(p)	**2.878* (0.027*)**	**1.769 (0.142)**
Residence		
Rural	2.95±5.18	17.75±2.45
Urban	3.73±4.84	18.85±2.57
t(p)	**0.632 (0.529)**	**1.730 (0.087)**
Occupation		
Not work	3.70±4.79	18.06±2.59
Manual work	5.89±5.86	20.17±2.43
Housewife	0.20±0.41	19.33±1.63
F(p)	**6.202* (0.003*)**	**5.980* (0.004*)**

F: One way ANOVA test t: Student t-test *: Statistically significant at $p \leq 0.05$

Table (7): Relation between Clinical data and study variables (n= 100).

Clinical data	Overall knowledge scale	Overall Signs and symptoms
Medical diagnosis		
Multinodular goiter	3.03±4.94	18.19±2.38
Follicular neoplasm	2.95±3.72	19.24±2.47
Papillary thyroid carcinoma	4.17±4.39	18.92±2.39
Graves' disease	4.23±5.65	18.57±2.86
F(p)	**0.505 (0.680)**	**0.759 (0.520)**
Experienced symptoms		
Swelling of the neck	2.06±3.79	19.0±2.49
Hoarseness	4.21±5.18	18.30±2.58
Difficulty of swallowing	3.97±5.25	18.97±2.67
Nervousness and irritability	13.0±0.0	15.50±2.12
Palpitation	3.0±1.73	17.0±0.0
F(p)	**3.086* (0.020*)**	**1.503 (0.208)**
Past medical history		
Diabetes Mellitus	3.55±4.98	19.24±2.12
Hypertension	4.53±5.49	17.20±2.67
Cardiovascular disorders	0.0±0.0	19.33±2.89
Endocrine disorders	2.25±4.37	20.88±0.35
Rheumatoid arthritis	2.09±1.58	19.91±1.87
F(p)	**1.188 (0.321)**	**7.424* (<0.001*)**
Age of onset of thyroid enlargement		
3<6 months	3.11±4.80	17.77±2.52
6<12 months	4.69±5.0	20.72±1.03
t(p)	**1.472 (0.144)**	**8.306* (<0.001*)**
Family past medical history		
Diabetes Mellitus	3.39±4.69	19.08±2.02
Hypertension	3.47±5.37	18.37±2.71
Cardiovascular disorders	7.40±6.07	19.40±2.19
Gastrointestinal disorders	3.0±2.83	19.0±2.83
Endocrine disorders	2.33±4.0	16.56±3.40
Cancer	3.72±4.76	18.94±2.71
F(p)	**0.740 (0.595)**	**1.668 (0.150)**
Types of family cancer		
Non	3.55±4.96	18.88±2.60
Colon	5.00±4.99	17.38±3.38
Breast	0.09±0.30	18.73±1.49
Head and neck	7.13±4.94	17.50±2.33
F(p)	**3.791* (0.013*)**	**1.399 (0.248)**
Relative degree		
Non	3.36±4.92	18.86±2.54
First degree	2.73±5.12	18.82±2.27
Second degree	5.54±4.33	17.15±2.64
F(p)	**1.298 (0.278)**	**2.545 (0.084)**
Used treatment method		
Radiotherapy	3.82±4.81	18.57±2.37
Surgery and radiotherapy	3.25±5.03	18.70±2.83
t(p)	**0.578 (0.564)**	**0.256 (0.798)**
Previous surgery		
No	4.20±5.09	18.51±2.70
Yes	0.25±0.68	19.25±1.61
t(p)	**6.804* (<0.001*)**	**1.477 (0.149)**
Site of tumor		
Oral cavity	4.06±5.39	17.35±2.61
Larynx	5.05±4.84	20.40±1.47
Oropharynx	0.43±0.51	20.07±1.54
Maxilla	0.67±1.03	19.0±1.55
Hypopharynx	4.50±4.93	20.50±1.22
F(p)	**2.811* (0.030*)**	**10.612* (<0.001*)**

F: One way ANOVA test t: Student t-test *: Statistically significant at $p \leq 0.05$

Table (8): Relation between Clinical data and study variables (n= 100).

Clinical data	Overall knowledge	Overall Signs and symptoms
Time of disease diagnosis		
< 2 months	2.72±4.75	20.78±0.94
2-6 months	3.76±4.93	18.16±2.57
t(p)	**0.811 (0.419)**	**7.258* (<0.001*)**
Mode of treatment		
Chemoradiation	3.30±4.92	18.41±2.61
Radiation alone	5.38±4.43	20.08±1.75
t(p)	**1.443 (0.152)**	**2.220* (0.029*)**
Chemo regimen		
Weekly CDDP	4.01±4.95	17.97±2.70
3 Weekly CDDP	4.00±5.54	21.0±0.0
Weekly Carboplatin	0.33±0.78	18.67±1.44
F(p)	**3.116* (0.049*)**	**12.834* (<0.001*)**
Radiation dose		
<60 Gy	0.22±0.67	18.33±1.0
60 Gy	0.64±0.50	20.71±1.07
>60 Gy	4.49±5.22	18.29±2.71
F(p)	**6.680* (0.002*)**	**5.889* (0.004*)**
Follow up		
6 months	3.44±4.88	18.43±2.59
9 months	0.80±1.10	20.40±1.34
12 months	10.0±2.0	21.0±0.0
F(p)	**4.607* (0.012*)**	**3.317* (0.040*)**

F: One way ANOVA test t: Student t-test *: Statistically significant at $p \leq 0.05$

Table (9): Stepwise Linear Regression Analysis Showing the Effect of different variables on Overall Signs and symptoms scale (n =100)

	B	Beta	t	p	95% CI	
					LL	UL
Step 1						
Age	1.376	0.565	6.775*	<0.001*	0.973	1.780
R^2= 0.319, Adjusted R^2= 0.312, F= 45.898*,p<0.001*						
Step 2						
Age	1.079	0.443	5.572*	<0.001*	0.695	1.463
Age of onset of thyroid enlargement	2.153	0.382	4.811*	<0.001*	1.265	3.041
R^2= 0.450 , Adjusted R^2= 0.439, F= 39.707*,p<0.001*						
Step 3						
Age	1.166	0.478	6.286*	<0.001*	0.798	1.534
Age of onset of thyroid enlargement	2.096	0.372	4.933*	<0.001*	1.253	2.940
Past medical history	0.345	0.247	3.427*	0.001*	0.145	0.545
R^2= 0.510, Adjusted R^2= 0.495, F= 33.318*,p<0.001*						

F,p: f and p values for the model R^2: Coefficient of determination
B: Unstandardized Coefficients Beta: Standardized Coefficients
t: t-test of significance LL: Lower limit UL: Upper Limit
*: Statistically significant at $p \leq 0.05$

Excluded Variables	Beta In	t	Sig.	Partial Correlation	Collinearity Statistics
					Tolerance
Occupation	0.014	0.183	0.855	0.019	0.867
Site of tumor	0.121	1.523	0.131	0.154	0.796
Time of disease diagnosis	-0.119	-1.384	0.170	-0.141	0.681
Moe of treatment	-0.109	-1.327	0.188	-0.135	0.749
Chemo regimen	0.072	0.941	0.349	0.096	0.877
Radiation dose	-0.033	-0.447	0.656	-0.046	0.941
Follow up	0.125	1.732	0.086	0.175	0.956
Overall . Knowledge	-0.083	-1.032	0.305	-0.105	0.797

Discussion:

Head and neck cancer includes otolaryngological cancer, oral and maxillofacial cancer, and neck cancer, which account for approximately 6% of all malignant cancer worldwide. Although head and neck cancer (HNC) is the sixth most common cancer worldwide, Egyptian studies reveal variations of incidence. In a data-base study, head and neck squamous cell carcinoma (HNSCC) constituted about 17-20% of all malignancies of El Gharbeya Governorate Hospitals, while in the cancer registry of Ain Shams University constitutes about 8% of the total malignancies **(Salem et al., 2016)**.

Radiotherapy was the most commonly used non-surgical therapy for locally advanced disease. But Radiotherapy with concurrent chemotherapy has been found to be superior to radiotherapy alone in the management of locally advanced head and neck cancers. This is because chemotherapeutic agents may both sensitize the cells to radiation and may also produce additional cytotoxicity **(Bray et al., 2018)**. The use of radiotherapy with concurrent chemotherapy resulted in reduction in risk of death and improvement in 5-year survival in patients of head and neck cancer. Radiotherapy is the main treatment modality for head and neck cancer, and the patients' neck is often included in the radiation field when receiving radiotherapy, resulting in damage to the normal tissue of the neck, especially radiation-induced hypothyroidism **(Immanuel et al., 2019).**

Hypothyroidism is a common complication that can occur after radiation therapy for head and neck cancers. The thyroid gland is particularly vulnerable to the damaging effects of radiation, which can result in a decrease in thyroid hormone production and the development of hypothyroidism. This in turn can lead to impairments in quality of life, including altered general body metabolism, decreased general health perception, worse emotional well-being, cognitive impairment, fatigue, and sexual dysfunction, among others. Furthermore, impaired thyroid function has been associated with increased overall risk of mortality **(Rooney et al., 2023)**. Treatment for hypothyroidism often requires lifelong hormone replacement, which itself can contribute to worse perceived quality of life and financial burden not only via direct medication costs but also due to recurrent healthcare visits and laboratory testing. Importantly, thyroid replacement therapy also may be ineffective in as many as 20% of patients due to a variety of causes such as gastrointestinal disease, drug interaction, and non-compliance **(Bano et al., (2017)**.

The findings of the present study revealed that there vast majority of the patients were males, from urban area and smokers this may be due to in Egypt males are the most persons exposed to direct, indirect smoking and occupational hazard that it can be risk factors of (HNC). This finding agrees with (**Moawad et al., 2023) who stated that** in Egypt, where cigarette and water pipe smoking rates have recently increased. In their population-based study, high HNC incidence among males and in urban populations.

This result was parallel with (**Barsouk et al., 2023) and (Yuriko.,2016)** who stated that Many different factors are associated with an increased risk of head and neck cancer, including tobacco, alcohol, diet, dental factors and human papillomavirus infection, either individually or in combination. Among them, cigarette smoking is one of the established causes for head and neck cancer. The International Agency for Research on Cancer (IARC) concluded that cigarette smoking was classified as Group 1: carcinogenic to humans, and that there was sufficient evidence for the association between cigarette smoking and head and neck cancer. It is based on the fact that cigarette smoking contains various carcinogens, resulting in genetic alterations leading to cancer.

Concerning age, the results of the current study revealed that more than half of the (HNC) patients were aged from 50 to less than 60 years. This finding may be due to that aging process is the biggest risk factor for (HNC) due to a number of structural, physiological and immunological changes with age. This finding supported **(NCCN ., 2024)** by Head and neck cancers are more common after the age of 40. Men are about 3 times more likely than women to develop a head and neck cancer, mainly due

to higher smoking and drinking rates.. The study also supported by (**Kouka et al., 2023**) who reported that Patients with head and neck cancer (HNC) are nearly 60% already over 60 years old and, approximately 70% are over 65 years and 50% over 70 years old.

Regarding the level of education, the finding of the present study showed that the highest percentage of (HNC) patients were illiterate this may be justified that the setting of the present study was free non-governmental and charity hospital and the majority of patients didn't work and all of them had low economical standards, while educated or highly educated patient are treated in private hospitals or in health insurance hospitals. This finding is explained by (**Kehinde and Kanmodi ., 2018).**

Regarding occupation and income the highest percentage of study and control group were retired and all of them not have enough income as the most of the studied patients have an early retirement due to the disease, because consequences and treatment schedule affect their work production. The result of this study was in agreement with **(Sesto et al., 2013)** who found that cancer survivors had a greater risk for early retirement as well as unemployment. Around half of cancer survivors may experience treatment- or disease-related long-term and late effects that can adversely impact work activities, with increased physical or cognitive demands can be particularly problematic for cancer survivors to perform Treatment related side effects such as fatigue, pain, and physical and cognitive limitations, in combination with age-related physical and cognitive changes, may exacerbate work-related difficulties for cancer survivors. Furthermore, from the researcher's view the high cost of treatment expenses, high cost of the basic human requirement for life and imbalance between income and outlay is the main causes of increase burden of (HNC) and chemo radiation side effects.

As regard to patients family history the present study revealed that, around half of (HNC) patients had family history of cancer. This finding was explained by(**Li et al., 2021)** who stated that When a parent or sibling was diagnosed with HNC, other family members had a two-fold risk of being diagnosed with HNC as genetic factors play a role in cancer cell development; abnormal chromosomal patterns and cancer have been associated with extra chromosomes change.

Also, the present study revealed that the highest percentage of studied patients had hypertension and had previous surgery. This result could be justified by that the majority of the sample were in the age group from50- 60 years old they are liable to develop chronic diseases in addition to the burden and stress of (HNC), this study contradicts with **(Abd-Elhamid, 2014)** who found that most of studied patients had a negative history of other associated diseases as hypertension, congestive heart failure and diabetes mellitus.

The study also revealed that all patients had Hypothyroidism, and received chemo radiation as a line of treatment from months to 1year, patients who receive radiotherapy to the neck are at increased risk of developing thyroid dysfunction, which is usually seen in the form of biochemical hypothyroidism but may also present as clinical hypothyroidism or thyrotoxicosis. These patients are also more likely to develop both benign and malignant nodules of the thyroid gland. Thyroid dysfunction after radiation is most often manifested by elevated serum concentration of Thyroid stimulating hormone (TSH).

This study in accordance with **(Akgun et al., 2014)** who stated that the incidence of hypothyroidism and the time after which it develops following radiation, tends to vary. According to 10% patients developed hypothyroidism within 6 months of radiotherapy and 23% developed hypothyroidism within 12 months of completion of radiotherapy. At a median follow up of 47 months, 52% patients were found to be hypothyroid. Also the study supported by **(Kim et al., 2014)** who stated that 46% patients developed hypothyroidism at a median period of 8 months after completion of radiotherapy. **(Weissler and Berry, 1991)** who reported that 57% of patients developed elevated TSH levels after radiotherapy. **(Banipal et al., 2011)** who found that TSH elevation in 75.4% patients who received

radiation for the treatment of head and neck cancers.

This study revealed that the highest percentage of patients received radiation dose >60 Gy.This study supported by **(Bhandare et al., 2007)** who reported that significantly higher incidence of hypothyroidism was found in patients receiving a mean thyroid gland dose more than 45 Gy. The study also in accordance with **(Sachdev et al., 2017)**who found that V50 > 60% puts patients at a significantly higher risk of becoming hypothyroid. Thyroid volume is a significant prognostic factor in the development of radiation induced hypothyroidism, with an increased risk at lower thyroid volumes.

The stud also supported by **(Alterio et al.,2007)**who showed that smaller thyroid volume was associated with higher incidence of thyroid toxicity. And in accordance with **(Boomsma et al., 2012)** who reported that the probability of hypothyroidism increased with increase in mean dose and decreased with higher thyroid gland volume. Thyroid disorders after radiation therapy to the neck still represent a clinically underestimated problem.

The results showed that, there was statistical significant difference between socio – demographic characteristics) and patients overall knowledge score, this study supported by **(Almuzaini et al., 2019)** who stated that there is a significant difference between genders and patients over all knowledge. The study contradict with **(Almuzaini et al., 2019)** who stated that there is no significant difference between gender in the level of knowledge.

The study showed that, there was statistical significant difference between socio – demographic characteristics (Age and Occupation) and patients **Overall Signs and symptoms**, this is contradict with (**Immanuel et al., 2019**)who stated that there is No association was seen between gender and mode of treatment and thyroid dysfunction. While the results is supported with (**Zhou1 L,etal 2021)** who stated that radiation-induced hypothyroidism is related to radiotherapy, (including thyroid dose-volume thresholds, pituitary dosevolume thresholds, and radiotherapy technique), chemotherapy, surgical treatment, and other clinical factors (such as sex, age, clinical stage.

The study revealed that, there was statistical significant difference between clinical data (**Time of disease diagnosis, Mode of treatment** ,**Chemo regimen, and Radiation dose**) and patients **Overall Signs and symptoms this results supported by** (**Immanuel et al., 2019**) and (**Zhou1 L, et al., 2021) who stated** that There was a statistically significant decrease in free T3 levels at 6 months post completion of treatment(p value <0.05).There was a statistically significant decrease in free T4 levels from baseline at 3 months and 6 months (p value <0.05). The results also supported by (**Banipal et al., 2011**) who stated that higher mean dose (above 48Gy) and smaller volume of thyroid gland had significant association with the development of hypothyroidism. TSH levels were significantly higher at baseline in males than in females but there was no significant correlation between gender and thyroid dysfunction. There was no association between thyroid dysfunction and the primary site or dose-volume parameters V10-V50.

The study showed that, there was positive statistically significant correlation between patients' age, onset of thyroid enlargement, Past medical history and **overall Signs and symptoms**, this contradict with **(Aulakh et al., 2022) who reported that** Gender, age, tumor histology, or surgery did not demonstrate statistically significant correlation with hypothyroidism. Thyroid volume correlated with hypothyroidism development. 51.2% of patients with thyroid volume less than of 13 cm3 (median volume) developed hypothyroidism compared to 27.2% of patients with greater volume. In our study, higher age was associated with a greater risk of hypothyroidism. **(Srikantia et al., 2017) who** found that52.9% of the patients who developed hypothyroidism were between the age groups of 51 to 60 years and increasing age was correlated with an increased risk of hypothyroidism.

The study revealed that, there was partial positive statistically significant correlation between (Occupation, Site of tumor, Time of

disease diagnosis, Mode of treatment, Chemo regimen, Radiation dose, Follow up, overall knowledge) and patients **Overall Signs and symptoms this results supported by (Aulakh et al., 2022) who stated that** Mean thyroid radiation dose also strongly correlated with hypothyroidism. 45.5 % of patients with mean thyroid dose greater than 40Gy developed hypothyroidism while 20.5% of those receiving less than 40Gy did not ($p < 0.001$). Chemotherapy also correlated with hypothyroidism ($p = 0.005$). Tumor site also correlated ($p = 0.007$) with oropharyngeal and laryngeal cancers demonstrating higher incidence.

However, the study contradicts with **(Alterio et al., 2007)** who did not find any correlation between treatment dose and thyroid dysfunction. The incidence of hypothyroidism in the RT alone group was 33.33% and in the chemoradiation group it was 17.14%. However, this difference was not found to be statistically significant. The also supported by (Kim et al.,2014) who stated that there was a positive correlation between higher mean dose to the thyroid and thyroid dysfunction.

The study also supported by (Marcella A et al., 2020) and and (Lollert et al., 2016) Studies in patients treated for malignancies involving the head and neck have shown a correlation between thyroid gland radiation dose and degree of reduction of thyroid gland volume. A study in 45 patients undergoing treatment with radiotherapy for nasopharyngeal carcinoma reported that a thyroid mean radiation dose of 43.9 Gy (range 23.3–58.6) was associated with a nearly 30% loss of thyroid volume in the first 12 months after radiotherapy. This study also showed that the level of serum free T4 declined as the thyroid volume decreased, with the highest occurrence of hypothyroidism at 24 months after treatment.

The study contradicts with **(Luo et al., 2018)** and **(Lee., etal2016)** who found that there is no correlation between chemotherapy and hypothyroidism. While the study supported by (**Ling et al., 2017**) who showed that chemotherapy is an independent risk factor for radiation-induce hypothyroidism, which was consistent with the results of Ling et al. Hypothalamus-pituitary dysfunction often occurs in patients after radiotherapy, resulting in central hypothyroidism, for which concurrent chemotherapy is a risk factor, which increases with time.

The symptoms of thyroid dysfunction may go unnoticed under the cover of other associated co-morbidities and side effects of the treatment modalities. Regular testing of thyroid function in patients undergoing radiation or chemo radiation can help in diagnosing thyroid dysfunction at the subclinical stage, before it progresses to clinical hypothyroidism. Larger multi-institutional studies with longer follow-up are needed to study the morbidity associated with post radiation thyroid dysfunction further (**Immanuel et al., 2019**).

Conclusion and recommendations:

Hypothyroidism is considered a relatively common late RT adverse effect for HNSCC patients. Regular post treatment assessment of thyroid function is recommended for HNSCC patients who received RT. The prevalence of HNC and its various types has grown in Egypt in recent years. This requires more focus from the research points on discussing various aspects of HNC, such as etiologies, risk factors, treatment, early diagnosis, screening, and prevention of causes.

- Research outputs should be increased in the field of HNC at different universities in Egypt, multicenter studies should be done, and collaboration programs with foreign centers should be implemented.
- Multicenter studies should be promoted to develop a collaborative research environment and provide a thorough understanding of HNC.
- A multidisciplinary approach, incorporating findings from other domains to create a comprehensive understanding of HNC, might enhance these investigations. Furthermore, collaborative projects with foreign institutes should be pushed aggressively. Such collaborations can enhance information exchange, give access to sophisticated research approaches, and contribute to the worldwide conversation around HNC. To address the growing

frequency of HNC in Egypt, a concerted effort comprising greater research output, multicenter and interdisciplinary investigations, and international cooperation is required. This strategic

Declaration of interest:

The contents of the paper and the opinions expressed within are those of the authors, and the authors decided to submit the manuscript for publication. All authors report no conflicts of interest relevant to this work.

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