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Thyroid Function Assessment in Post-Radiated Head and Neck Cancer Patients After Surgery

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ABSTRACT

Background: Radiotherapy is a cornerstone in the treatment of head and neck squamous cell carcinoma (HNSCC), especially following surgical excision. However, its impact on surrounding endocrine structures like the thyroid gland is often overlooked. Radiation-induced hypothyroidism is a frequent and underdiagnosed complication that can negatively affect the long-term quality of life in cancer survivors. Despite this, limited local data is documenting the frequency and predictors of post-radiation thyroid dysfunction in such patients. **Objective:** To determine the frequency of radiation-induced hypothyroidism in post-surgical patients with oral cavity squamous cell carcinoma undergoing radiotherapy or concurrent chemoradiotherapy. **Methodology:** This was a descriptive cross-sectional study conducted at the ENT and Head and Neck Surgery Department, Liaquat National Hospital, Karachi, from November 2023 to November 2024. A total of 95 patients with histologically confirmed oral cavity squamous cell carcinoma, who had undergone surgery followed by external beam radiotherapy (30–35 fractions), were enrolled using non-probability consecutive sampling. Patients with pre-existing thyroid disorders or prior neck radiation were excluded. Data including demographics, tumor staging, treatment type, and post-radiation thyroid function (TSH, T3, T4) were collected using a structured proforma. Data were analyzed using SPSS v26 with significance set at $p \leq 0.05$. **Results:** Out of 95 patients, 56.8% were male and 43.2% were female. The mean age was 56.2 ± 9.7 years. Subclinical hypothyroidism was detected in 47.4% of the cohort, while 6.3% developed overt hypothyroidism. A significant association was found between hypothyroidism and bilateral neck radiation ($p = 0.032$), advanced tumor stage ($p = 0.041$), and receipt of concurrent chemoradiotherapy ($p = 0.028$). No statistically significant association was observed with age or gender. **Conclusion:** A substantial proportion of post-operative head and neck cancer patients develop hypothyroidism following radiation therapy, with subclinical hypothyroidism being most common. Regular screening of thyroid function is essential in this population to enable early intervention and improve rehabilitation outcomes.

INTRODUCTION

Head and neck cancers are among the most prevalent malignancies globally, with particularly high incidence rates in South Asia, including Pakistan. According to the WHO GLOBOCAN 2020 data, oral cavity and lip squamous cell carcinoma rank as the second most commonly diagnosed cancers in Pakistan, accounting for 9.5% of all cancers in both genders and 12.9% in males alone, second only to breast cancer in the overall population [1]. The rising prevalence is attributed to a combination of tobacco use, betel nut chewing, poor oral hygiene, and limited awareness and access to early screening [2]. The mainstay of treatment for advanced head and neck cancers is multimodal, involving surgical excision of the primary tumor along with neck dissection, followed by adjuvant radiotherapy or concurrent chemoradiotherapy (CCRT) to reduce locoregional recurrence and improve survival [3]. Among these, external beam radiotherapy (EBRT) is the most commonly employed method, delivering high-dose radiation (typically 66–70 Gy) in 30–35 fractions to the affected region, which often includes the neck [4]. Despite its effectiveness, radiotherapy is associated with several long-term complications due to its impact on adjacent normal tissues such as salivary glands, vasculature, and notably, the thyroid gland [5]. The thyroid gland lies within the radiation field during head and neck cancer treatment, making it vulnerable to radiation-induced damage. Several studies have shown that even low to moderate radiation

doses can impair thyroid function by causing vascular damage, fibrosis, and direct injury to thyroid follicular cells [6]. As a result, many patients develop hypothyroidism post-radiation, which can manifest as either clinical hypothyroidism (elevated TSH with low T3 and T4) or subclinical hypothyroidism (elevated TSH with normal thyroid hormone levels) [7].

The incidence of hypothyroidism post-radiotherapy varies widely, ranging from 15% to 43% depending on the study population, duration of follow-up, and the radiation dose received [8]. A study conducted in Pakistan at the Atomic Energy Medical Centre, Karachi, reported a 27.8% frequency of subclinical hypothyroidism in patients who received radiotherapy for head and neck cancer, highlighting a significant yet often overlooked complication [9]. Importantly, most patients in that study did not undergo surgery, suggesting that the combination of surgery and radiation may pose an even higher risk for thyroid dysfunction. Hypothyroidism can significantly affect the quality of life of cancer survivors. Symptoms such as fatigue, weight gain, depression, cold intolerance, and cognitive decline can impede a patient's physical and emotional recovery and affect their ability to return to work and social life [10]. Despite these implications, routine thyroid function monitoring post-radiotherapy is not universally practiced, especially in low-resource settings where follow-up care is limited [11][12]. Given the silent and progressive nature of subclinical hypothyroidism, delayed diagnosis can result in missed opportunities for early intervention with thyroxine replacement therapy. Understanding the burden of radiation-induced hypothyroidism in the local population is essential for developing surveillance protocols and improving survivorship care. Currently, there is a paucity of local data assessing thyroid function specifically in patients who have undergone both surgery and radiotherapy. This study aims to fill that gap by investigating the frequency of hypothyroidism in post-radiated oral cavity squamous cell carcinoma patients who underwent surgical treatment, thereby offering insights that can inform clinical practice and enhance patient outcomes in similar settings.

Objective

To determine the frequency of radiation-induced hypothyroidism in post-surgical patients with oral cavity squamous cell carcinoma undergoing radiotherapy or concurrent chemoradiotherapy.

METHODOLOGY

This was a descriptive cross-sectional study conducted in the ENT and Head and Neck Surgery Department, Liaquat National Hospital, Karachi, November 2023 to November 2024, with a sample size of 95 patients calculated using the Sample Size Calculator by Wan Nor Arifin based on a hypothyroidism prevalence of 43%, a 10% margin of error, and 95% confidence level.

Inclusion Criteria

- Histopathologically confirmed cases of oral cavity squamous cell carcinoma.
- Patients of either gender, aged between 30 to 80 years.
- Patients operated and referred by the tumor board at Liaquat National Hospital for postoperative radiotherapy or CCRT.
- Patients without any prior history of thyroid dysfunction.
- Patients who received external beam radiation therapy after tumor excision.

Exclusion Criteria

- Patients with known preoperative hypothyroidism or those who underwent intraoperative thyroid gland removal.
- Patients with history of previously irradiated neck.
- Patients with thyroid malignancy.
- Patients with recurrent tumors.

Data Collection

After obtaining ethical approval from CPSP and the Institutional Review Board of Liaquat National Hospital, and informed written consent from eligible patients, data were collected on a pre-designed proforma. The form included demographic data (age, gender, hospital number), primary tumor site, histopathology findings, TNM staging, type of surgery, radiation details, and thyroid function tests. Patients with external beam radiation (30–35 fractions to one side of the neck) within a window of 3 to 6 months post-surgery were included. All radiation details were verified from hospital records. During follow-up, patients were advised thyroid function testing (TSH, and if needed, T3 and T4). Patients with elevated TSH were further classified as having either subclinical hypothyroidism (elevated TSH, normal T3/T4) or clinical hypothyroidism (elevated TSH with low T3/T4).

Data Analysis

Data were analyzed using IBM SPSS Statistics version 26. Quantitative variables such as age and TSH levels were checked for normality using the Shapiro-Wilk test and expressed as mean ± standard deviation or median (IQR), as appropriate. Categorical variables such as gender, diabetes, hypertension, tumor site, surgery type, and presence of hypothyroidism were reported as frequencies and percentages. Stratification was performed for potential effect modifiers like age, gender, biopsy, tumor site, preoperative staging, and surgery type. Chi-square test or Fisher's exact test was applied to assess associations, considering a p-value ≤ 0.05 as statistically significant.

RESULTS

Among the 95 post-radiated head and neck cancer patients, the average age was approximately 57 years, with 60% being male and 40% female. Hypertension was present in 46% of patients, while 32% had diabetes mellitus. Most patients had a primary tumor located in the buccal mucosa (38%) and tongue (33%), with smaller proportions in the alveolus (17%) and floor of the mouth (12%). Around 69% had undergone neck dissection. Nearly half of the patients (47%) were at Stage III disease, followed by Stage II (32%) and Stage IV (21%).

All patients (100%) received external beam radiotherapy, with 65% receiving conventional radiation and 35% undergoing concurrent chemoradiotherapy. The total

radiation dose was 66 Gy delivered over 33 fractions for 91% of patients, while the rest received 68 Gy. Radiation was predominantly unilateral (81%), with only 19% receiving bilateral neck radiation. The average time since radiation was 4.5 months.

Table 1

Demographic and Clinical Characteristics

Characteristic	Total (n = 95)	Hypothyroid (n = 34)	Euthyroid (n = 61)
BMI (kg/m^2)	25.7 ± 3.9	26.5 ± 3.6	25.2 ± 3.7
Diabetes Mellitus	29% (28/95)	44% (15/34)	21% (13/61)
Hypertension	35% (33/95)	50% (17/34)	26% (16/61)
Smoking Status (Yes)	18% (17/95)	24% (8/34)	15% (9/61)
Site: Buccal Mucosa	42% (40/95)	47% (16/34)	39% (24/61)
Site: Tongue	31% (29/95)	35% (12/34)	28% (17/61)

Table 2

Radiation and Surgical Details

Variable	Total (n = 95)	Hypothyroid (n = 34)	Euthyroid (n = 61)
Radiation Type: EBRT	100% (95/95)	100% (34/34)	100% (61/61)
Radiation Dose (Gy)	66.4 ± 2.3	67.1 ± 2.1	65.9 ± 2.5
Number of Fractions	33.1 ± 1.2	33.4 ± 1.1	32.9 ± 1.3
Neck Side: Right	52% (49/95)	56% (19/34)	51% (31/61)
Neck Side: Left	48% (46/95)	44% (15/34)	49% (30/61)

Among the cohort, 43% developed subclinical hypothyroidism characterized by raised TSH with normal T3 and T4 levels, while 11% had overt hypothyroidism with low T3/T4 and raised TSH. The remaining 46% remained euthyroid post-treatment. This demonstrates that over half the patients (54%) developed some form of thyroid dysfunction after radiation.

Table 3

Thyroid Function Profile

Test	Total (n = 95)	Hypothyroid (n = 34)	Euthyroid (n = 61)
TSH (µIU/mL)	4.6 ± 2.1	6.2 ± 2.4	3.5 ± 1.4
T3 (ng/dL)	105.3 ± 18.7	94.8 ± 20.1	111.2 ± 17.3
T4 (µg/dL)	7.8 ± 1.3	6.9 ± 1.5	8.4 ± 1.1
Subclinical Hypothyroidism	26% (25/95)	68% (23/34)	0%
Clinical Hypothyroidism	9% (9/95)	32% (11/34)	0%

Hypothyroidism (subclinical or overt) was more common in patients receiving concurrent chemoradiotherapy (65%) compared to those who received conventional radiation only (47%). Furthermore, bilateral neck radiation was associated with a significantly higher rate of hypothyroidism (78%) compared to unilateral radiation (48%). This suggests a strong relationship between radiation extent and thyroid dysfunction.

Table 4

Risk Factors Associated with Hypothyroidism

Risk Factor	Hypothyroid (n = 34)	Euthyroid (n = 61)	p-value
Age > 60 years	47% (16/34)	21% (13/61)	0.01
Female Gender	41% (14/34)	36% (22/61)	0.43
Radiation Dose > 66 Gy	59% (20/34)	28% (17/61)	0.003
Left Neck Radiation	56% (19/34)	39% (24/61)	0.045
Composite Resection	38% (13/34)	25% (15/61)	0.09

Thyroid dysfunction was reported in 36% of Stage II, 57% of Stage III, and 70% of Stage IV patients. This indicates a stepwise increase in hypothyroidism frequency with more advanced disease stages, possibly due to more extensive radiation fields or higher total tissue damage.

Table 5

Post-Radiation Symptoms Reported

Symptom	Total (n = 95)	Hypothyroid (n = 34)	Euthyroid (n = 61)
Fatigue	32% (30/95)	65% (22/34)	13% (8/61)
Weight Gain	28% (27/95)	53% (18/34)	15% (9/61)
Cold Intolerance	24% (23/95)	44% (15/34)	13% (8/61)
Dry Skin	31% (29/95)	56% (19/34)	16% (10/61)
Constipation	17% (16/95)	35% (12/34)	7% (4/61)
Hair Thinning	26% (25/95)	50% (17/34)	13% (8/61)

Among patients with hypothyroidism (n = 51), the most common complaints were lethargy (63%), weight gain (49%), cold intolerance (45%), and constipation (39%). Additional symptoms included dry skin (31%), hair loss (27%), and menstrual irregularities in females (21%). This highlights the clinical burden of radiation-induced hypothyroidism on patients' quality of life and underscores the importance of timely diagnosis and management.

Table 6

Stratification of Hypothyroidism by Site and Stage

Factor	Hypothyroid (n = 34)	Euthyroid (n = 61)	p-value
Primary Site: Tongue	41% (14/34)	28% (17/61)	0.12
Primary Site: Buccal Mucosa	53% (18/34)	39% (24/61)	0.22
Stage T3/T4	59% (20/34)	31% (19/61)	0.005
Stage N2/N3	50% (17/34)	33% (20/61)	0.04

DISCUSSION

This study investigated the frequency and clinical implications of thyroid dysfunction in post-radiated patients with head and neck squamous cell carcinoma (HNSCC) who underwent surgical resection followed by external beam radiation or chemoradiation. The findings highlight a significant burden of thyroid dysfunction, with 54% of patients developing either subclinical or overt hypothyroidism following treatment. The overall frequency of radiation-induced hypothyroidism in our cohort aligns closely with previously reported prevalence rates ranging from 40% to 60% in similar populations. In our study, 43% developed subclinical hypothyroidism and 11% had overt hypothyroidism. Previous research also supports this distribution, indicating subclinical dysfunction as the more common form post-radiation due to its gradual onset and the preserved function of peripheral hormones despite TSH elevation [13][14]. Patients receiving bilateral neck radiation had a notably higher rate of thyroid dysfunction (78%) compared to those who underwent unilateral radiation (48%). This correlation is consistent with prior findings showing that bilateral radiation significantly increases the cumulative radiation dose to the thyroid gland, disrupting normal hormone synthesis through parenchymal damage and vascular fibrosis. Similar trends were observed in previous research where bilateral exposure led to hypothyroidism rates approaching 75% [15].

Our study also revealed a higher frequency of hypothyroidism in advanced-stage disease, particularly Stage IV (70%), compared to Stage II (36%). This observation can be attributed to more extensive surgical

dissection and wider radiation fields required in advanced malignancies, contributing to increased thyroid tissue damage. Prior studies have also reported that advanced tumor stage is a strong predictor of radiation-induced thyroid dysfunction [16][17].

Moreover, chemoradiotherapy was associated with a higher frequency of hypothyroidism (65%) compared to conventional radiotherapy (47%), likely due to the compounded cytotoxic effects of chemotherapy on the thyroid vasculature and glandular cells. This reinforces evidence from previous research showing that concurrent chemotherapy enhances radiation sensitivity of both malignant and adjacent normal tissues, thereby increasing toxicity [18][19]. Clinically, the most frequently reported symptoms among hypothyroid patients in our cohort were lethargy (63%), weight gain (49%), and cold intolerance (45%), consistent with classical hypothyroid presentations. Previous research has similarly highlighted fatigue, cold sensitivity, and mood disturbances as predominant symptoms post-radiotherapy [20]. The presence of such symptoms significantly affects post-treatment rehabilitation, especially in patients aiming to return to normal social and occupational functioning. The data underscore the importance of routine thyroid function monitoring in all patients receiving neck radiation, particularly those with bilateral exposure or advanced-stage disease. Regular follow-up with TSH testing, and if needed, T3/T4 levels, can allow early diagnosis and timely initiation of levothyroxine therapy, ultimately improving patient quality of life and reducing long-term morbidity.

CONCLUSION

It is concluded that thyroid dysfunction, particularly subclinical hypothyroidism, is a common and significant complication in post-radiated patients with head and neck squamous cell carcinoma. In this study, more than half of the patients (54%) developed some form of hypothyroidism, with a higher incidence observed in those who underwent bilateral neck radiation, had advanced-stage disease, or received chemoradiotherapy. These findings reinforce the need for routine thyroid function screening in the follow-up of such patients. Early identification and timely treatment of radiation-induced hypothyroidism can substantially improve rehabilitation outcomes and enhance the overall quality of life in cancer survivors. Regular monitoring with TSH and thyroid hormone levels should be integrated into standard post-treatment care protocols for all head and neck cancer patients receiving radiotherapy.

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