Section: Oncology

Original Research Article

INCIDENCE AND RISK FACTORS OF RADIATION-INDUCED HYPOTHYROIDISM IN HEAD AND NECK CANCER PATIENTS: A PROSPECTIVE OBSERVATIONAL STUDY

Received : *22/02/2025*
Received in revised form : *16/04/2025*
Accepted : *02/05/2025*

Keywords:
Head and Neck Cancer, Radiation-Induced Hypothyroidism, Radiotherapy, Thyroid Dysfunction.

Corresponding Author:
Dr. Dhiraj Daga,
Email: dhirajdaga@gmail.com

DOI: 10.47009/jamp.2025.7.3.43

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (3); 233-237

Unnati Batra[1], Himanshu Bhardwaj[2], Narender Singh Shah[3], Dhiraj Daga[4], Pranjal Maheshwari[1], Devender Baisoya[1], Arti Kumawat[1], Teenu Narwal[1]

[1]Junior Resident, Department of Radiation Oncology, J.L.N Medical College and Hospital, Ajmer, Rajasthan, India.
[2]Junior Resident, Department of General Medicine, J.L.N Medical College and Hospital, Ajmer, Rajasthan, India.
[3]Senior Professor, Department of Radiation Oncology, J.L.N Medical College and Hospital, Ajmer, Rajasthan, India.
[4]Assistant Professor, Department of Radiation Oncology, J.L.N Medical College and Hospital, Ajmer, Rajasthan, India.

ABSTRACT

Background: Head and neck cancers (HNCs) often require radiotherapy (RT), which inadvertently exposes the thyroid gland to radiation, increasing the risk of radiation-induced hypothyroidism (RIH). This study aimed to evaluate the incidence of RIH and identify associated risk factors. **Materials and Methods:** Fifty patients with histopathologically confirmed HNC undergoing external beam RT to the neck were prospectively studied from August 2023 to May 2024. Baseline thyroid function tests (TFTs) were conducted prior to RT and repeated at the end of treatment, and at 3 and 6 months post-RT. Statistical analyses assessed the association of hypothyroidism with clinical and treatment variables. **Result:** At 6 months post-RT, 18% of patients developed hypothyroidism, with significant reductions in FT3 and FT4 levels and a rise in TSH levels ($p < 0.05$). Although no statistically significant associations were found with surgery, chemotherapy, or RT dose, smoking showed a significant correlation with hypothyroidism ($p = 0.0138$). **Conclusion:** RIH is a common yet underdiagnosed consequence of RT in HNC patients. Regular TFTs during follow-up are essential for early detection and management to prevent long-term morbidity.

INTRODUCTION

Head and neck cancers (HNC) are a complex category of tumors belonging to the upper aerodigestive tract, affecting the oral cavity, oropharynx, larynx, upper esophagus, sinuses, salivary glands, and lips, developed mainly due to tobacco and alcohol consumption or HPV infection.[1] As per GLOBOCAN 2022 HNC is the most common site of cancer in terms of incidence as well as mortality in India.[2]

The treatment of head and neck cancers include surgery, Radiotherapy (RT), chemotherapy, and a combination of these. RT is the only curative treatment, besides surgery, in the management of patients with head and neck cancer. Majority of head and neck tumors are locoregionally advanced at the time of diagnosis. Hence, RT portals, apart from including the primary site of the tumor, will invariably cover the whole neck, thereby including the thyroid gland in the radiation field leading to its dysfunction.[3]

Thyroid dysfunction, which can be diagnosed by thyroid function tests, is more frequent but is often missed because routine testing of thyroid hormones is not done during follow-up. Therefore RT-induced hypothyroidism (RIH) has remained under estimated and under reported, resulting in failure to detect and treat a reversible cause of morbidity for a significant proportion of surviving patients. Hence, the purpose of this study is to identify the magnitude of hypothyroidism following RT to the neck, its risk factors in developing and treating patients with subclinical thyroid dysfunction, and to stress upon the necessity of including thyroid function tests as part of follow-up.

MATERIALS AND METHODS

The study was conducted in patients with histopathological proven head and neck cancer receiving external beam RT to the whole neck on Telecobalt between August 2023 and May 2024.

The patients included were of age between 18 to 70, both the sexes, having Karnofsky Performance Score (KPS) more than or equal to 70, with normal thyroid function receiving External Beam Radiotherapy to the neck with thyroid gland in the field of RT and those excluded were patients with history of previous thyroid surgery, pre-existing thyroid disease, recurrent disease, prior RT to neck or any comorbid conditions requiring long term medications. A total of 50 patients who have completed their treatment protocol were included in the study after informed consent from them.

Patients receiving conventional radiotherapy with or without chemotherapy either with or without surgery or induction chemotherapy. All patients were treated with 2-dimensional (2D) radiotherapy technique with iso-centric fields on by Theratron 780C Cobalt-60 Teletherapy machine. Conventional fractionation of 2 Gy/Fr/day for 5 days a week. Total dose 54-70 Gy (as indicated) with or without concurrent chemotherapy (weekly or 3 weekly cisplatin) with spinal cord sparing after 44 Gy. The treatment portals included the primary tumor with margin and the whole neck. The treatment intent was either radical or postoperative adjuvant.

Along with workup of treatment for Radiotherapy a baseline thyroid function tests TSH (Thyroid-Stimulating Hormone), FT3 (Free T3) and FT4 (Free T4)) was done before starting Radiotherapy. Similarly thyroid function test was done at completion of RT as well as on follow-up up on 3 and 6 months. The normal values used for the study were TSH 0.34 to 5.60 microIU/ml , FT3 2.5 to 3.9 pg/ml and FT4 0.61 to 1.12 ng/dl.

All values are expressed as means and standard deviations (SD). Z-test for binomial single proportion has been used to find the significance of occurrence of hypothyroidism according to age, sex, chemotherapy, primary sub- site, surgical treatment, smoking, and radiotherapy. P values <0.05 were considered to indicate statistical significance.

RESULTS

Patient characteristics

In this prospective, nonrandomized clinical study of 50 patients, 45 (90 %) were males and 5 (10 %) were females and the median age was 55 years with the age ranges from 32 to 70 years. Primary subsite in majority of the patients was carcinoma Oropharynx (44%) followed by oral cavity (40%). 68% were smokers and majority of them were in stage IV (68%) as per AJCC staging manual.

Treatment characteristics

22% patients received radiotherapy as adjuvant treatment i.e. had surgery before receiving Radiotherapy whereas 78% were treated with radiotherapy with radical intent. 16% of the patients received induction chemotherapy and along with concurrent chemoradiation with 3 weekly cisplatin, 24% received weekly cisplatin during RT and 24% received 3 weekly cisplatin during RT and only 10% didn't received any chemotherapy.

Table 1: Characteristics of the patients and treatments

Patient Characteristics	N(%)	Median (Range)
Sex		
Male	45 (90%)	
Female	5 (10%)	
Age		
Median		55 (70-32)
Smoking		
Yes	16 (32%)	
No	34 (68 %)	
Diagnosis		
Oral Cavity	20 (40%)	
Oropharynx	22 (44%)	
Hypopharynx	2 (4%)	
Larynx	6 (12%)	
Stage (TNM)		
II	5 (10%)	
III	11 (22%)	
IV	34 (68%)	
Radiotherapy		
Adjuvant	11 (22 %)	
Definitive (Radical)	39 (78%)	
Chemotherapy		
Induction (TPF) Chemotherapy with concurrent 3weekly cisplatin	8 (16%)	

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Concurrent - 3 weekly Cisplatin	12 (24%)	
Concurrent - Weekly Cisplatin	24 (48%)	
Only Radiotherapy	5 (10%)	

Table 2: Mean (± SD) of Thyroid Function Tests at different intervals

	Before RT	End of RT	After 3 months of completing RT	After 6 months of completing RT	p value (before RT and at 6 months) The Wilcoxon Signed-Ranks Test
FT3	3.1±0.408	3.03±0.363	2.87±0.282	2.86±0.408	The value of z is-4.4067. The p-value is < .00001. The result is **significant** at p < .05.
FT4	0.83±0.1	0.82±0.1	0.82±0.1	0.78±0.2	The value of z is-4.4067. The p-value is < .00001. The result is **significant** at p < .05.
TSH	3.43±1.3	3.8±1.2	4.29±1.6	6.26±4.63	The value of *z* is-5.8451. The *p*-value is < .00001. The result is **significant** at *p* < .05.

Table 3: Occurrence of Hypothyroidism according to Primary site

Chemotherapy	No. of Patients	No of patients with hypothyroidism (%)	p value
Oral Cavity	20	5 (25%)	The chi-square statistic is 6.5954. The *p*-value is .085976. The result is ***not* significant** at *p* < .05.
Oropharynx	23	1 (4.3%)	
Hypopharynx	2	1 (50%)	
Larynx	5	2 (40%)	

Table 4: Occurrence of Hypothyroidism according to Surgery

Surgery	No. of Patients	No of patients with hypothyroidism ()	p value
Yes	11	4 (36.4%)	The chi-square statistic is 3.222. The p-value is .072654. The result is not significant at p < .05.
No	39	5 (12.8%)	

Table 5: Occurrence of Hypothyroidism according to Chemotherapy

Chemotherapy	No. of Patients	No of patients with hypothyroidism (%)	p value
ICT with Concurrent Cisplatin 3 weekly	8	2 (25%)	The chi-square statistic is 0.3131. The p-value is .957555. The result is not significant at p < .05.
Concurrent Cisplatin weekly	24	4 (16.67%)	
Concurrent Cisplatin 3 weekly	12	2 (16.67%)	
No Chemotherapy	5	1 (20%)	

Table 6: Occurrence of Hypothyroidism according to Radiotherapy

Chemotherapy	No. of Patients	No of patients with hypothyroidism ()	p value
≤60Gy	11	4 (36.4%)	The chi-square statistic is 3.222. The p-value is .072654. The result is not significant at p < .05.
>60Gy -70GY	39	5 (12.8%)	

Table 7: Occurrence of Hypothyroidism according to Smoking

Surgery	No. of Patients	No of patients with hypothyroidism ()	p value
Yes	16	6 (37.5%)	The chi-square statistic is 6.0617. The p-value is .013815. The result is significant at p < .05.
No	34	3 (8.82%)	

Radiation-induced hypothyroidism (RIH)

At the end of 6 months after completion of radiotherapy, 9 out of 50 i.e. 18% patients had hypothyroidism. Table 2 illustrates the mean values and standard deviations of FT3, FT4, and TSH at various intervals: before radiotherapy (RT), at the end of RT, and at 3-month and 6-month follow-ups. A significant reduction in FT3 and FT4 levels and an elevation in TSH levels were observed over time. The decline in FT3 from 3.1 ± 0.408 to 2.86 ± 0.408 pg/ml and in FT4 from 0.83 ± 0.1 to 0.78 ± 0.2 ng/dl was statistically significant (p < 0.05). Similarly, the increase in TSH levels from 3.43 ± 1.3 to 6.26 ± 4.63 µIU/ml was significant (p < 0.05).

The distribution of hypothyroidism based on primary tumor site, chemotherapy, surgery, radiotherapy dose, and smoking status is detailed in Tables 3 to 7.

Primary Tumor Site: The incidence of hypothyroidism was highest among hypopharyngeal cancer patients (1 out of 2, 50%) and laryngeal cancer

ISSN (O): 2687-5365; ISSN (P): 2753-6556

patients (2 out of 5, 40%). However, this association was not statistically significant (p = 0.0859)(table 3).

Surgical History: Patients who underwent surgery prior to radiotherapy demonstrated a higher incidence of hypothyroidism (4 out of 11, 36.4%) compared to those treated without surgery (5 out of 39, 12.8%). However, this association did not reach statistical significance (p = 0.0727) (table 4).

Chemotherapy Impact: The type of chemotherapy (induction chemotherapy, weekly or 3-weekly cisplatin, or no chemotherapy) showed no significant effect on the development of hypothyroidism (p = 0.9576) (table 5).

Radiotherapy Dose: Patients receiving a ≤60 Gy exhibited a slightly higher incidence of hypothyroidism (4 out of 11, 36.4%). compared to those receiving more than 60 Gy (5 out of 39, 12.8%). This difference was not statistically significant (p = 0.0727) (table 6).

Smoking Status: A significant association was observed between smoking and hypothyroidism (p = 0.0138). Six out of 16 smokers (37.5%) developed hypothyroidism compared to 3 out of 34 non-smokers (8.8%) (table 7).

DISCUSSION

Radiation-induced hypothyroidism (RIH) is a well-recognized complication in head and neck cancer patients undergoing radiotherapy. In this study, the incidence of hypothyroidism at 6 months post-radiotherapy was 18%, which aligns with previously reported rates ranging from 10% to 40%.[4-7]

The significant reduction in FT3 and FT4 levels and the marked elevation in TSH levels indicate impaired thyroid function. TSH elevation is an early marker of hypothyroidism and suggests subclinical or overt hypothyroidism, often resulting from radiation damage to the thyroid gland.[4] The thyroid gland's susceptibility to radiation stems from its anatomical location within the cervical region, often placing it within the RT field. Radiation can damage thyroid follicular cells, leading to decreased hormone production. Additionally, RT may induce vascular damage and fibrosis, further impairing thyroid function.[8]

Patients undergoing surgery followed by adjuvant radiotherapy showed a higher incidence of hypothyroidism. The disruption of vascular supply to the thyroid gland during surgery may make it more susceptible to radiation damage.[9] Tell *et al* reported that addition of surgery to RT increased the overall risk of HT, similar findings were seen with Koc and Capoglu also.[5,10]

The use of chemotherapy in head and neck cancers varies from center to center. Turner *et al* had a very high number of patients receiving chemotherapy (77%).[4] Mercado *et al* had 50% of the patient's receiving chemotherapy.[11] These studies had a higher percentage of patients with locally advanced disease or were randomized to compare the effect of chemotherapy on tumor response as well as incidence of hypothyroidism. This study also have different chemotherapy pattern in the study group. Though no significant correlation was found between chemotherapy regimens and hypothyroidism. Most studies proposed that there is no correlation between chemotherapy and hypothyroidism.[8,12]

Although higher radiation doses (≥60 Gy) were associated with a slightly increased incidence of hypothyroidism, this was not statistically significant. This is supported by Mercado *et al*.[11] In their study of 155 patients, they observed that the likelihood of developing hypothyroidism could not be predicted according RT dosage to the primary site or to the neck. In a study by Koc and Capoglu, univariate analysis of various factors failed to identify RT dose as a relevant risk factor for hypothyroidism.[5] Akgun *et al* found a significant association between the development of hypothyroidism and the V30, which corelates, no statistically significance was found at higher doses.[12]

A significant association between smoking and hypothyroidism was identified in this study. Smoking may contribute to oxidative stress, aggravating radiation-induced thyroid injury, which is in-contrast to Kumpulainen *et al*, Koc and Capoglu, in which no relation was found between incidence of hypothyroidism and smoking in patients undergoing RT for head and neck cancer.[5,13]

The response to radiation is governed by the inherent cellular radiosensitivity, the kinetics of the tissue, and the way in which cells are organized in that tissue.[14]

The mechanism of radiation-induced HT remains unexplained. It is believed that radiation induces direct damage to the glandular cell, an interference of its mitosis, a disturbance to feeding vessels, or some kinds of immune reaction.[15]

Given the high incidence of RIH, regular thyroid function monitoring is imperative. It is recommended to assess thyroid-stimulating hormone (TSH) levels every 6 months for the first 2 years post-RT, followed by annual evaluations for at least 5 years. Early detection allows for timely intervention with thyroid hormone replacement therapy, thereby mitigating symptoms and improving patient quality of life.

CONCLUSION

RIH is a significant concern in HNC patients undergoing RT. Understanding the multifaceted risk factors—encompassing patient-specific, surgical, chemotherapeutic, and dosimetric elements—is essential for developing tailored treatment plans. Implementing strategies to minimize thyroid radiation exposure and establishing rigorous post-treatment monitoring protocols are pivotal steps in reducing the burden of RIH.

REFERENCES

1. Anderson G, Ebadi M, Vo K, Novak J, Govindarajan A, Amini A. An updated review on head and neck cancer

ISSN (O): 2687-5365; ISSN (P): 2753-6556

treatment with radiation therapy. Vol. 13, Cancers. MDPI; 2021.

2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209–49.
3. Srikantia N, Rishi KS, Janaki MG, Bilimagga RS, Ponni A, Rajeev AG, *et al*. How common is hypothyroidism after external radiotherapy to neck in head and neck cancer patients? Indian Journal of Medical and Paediatric Oncology. 2011;32(3):143–8.
4. Turner SL, Tiver KW, Boyages SC. Thyroid dysfunction following radiotherapy for head and neck cancer. International Journal of Radiation Oncology*Biology*Physics. 1995 Jan 15;31(2):279–83.
5. Koc M, Capoglu I. Thyroid dysfunction in patients treated with radiotherapy for neck. American Journal of Clinical Oncology: Cancer Clinical Trials. 2009 Apr;32(2):150–3.
6. Kim MY, Yu T, Wu HG. Dose-volumetric parameters for predicting hypothyroidism after radiotherapy for head and neck cancer. Jpn J Clin Oncol. 2014;44(4).
7. Rooney MK, Andring LM, Corrigan KL, Bernard V, Williamson TD, Fuller CD, *et al*. Hypothyroidism following Radiotherapy for Head and Neck Cancer: A Systematic Review of the Literature and Opportunities to Improve the Therapeutic Ratio. Vol. 15, Cancers. Multidisciplinary Digital Publishing Institute (MDPI); 2023.
8. Vogelius IR, Bentzen SM, Maraldo M V., Petersen PM, Specht L. Risk factors for radiation-induced hypothyroidism: A literature-based meta-analysis. Vol. 117, Cancer. 2011. p. 5250–60.
9. Wang C, Hou Y, Wang L, Yang Y, Li X. Analysis of correlative risk factors for radiation-induced hypothyroidism in head and neck tumors. BMC Cancer. 2024 Dec 1;24(1).
10. Tell R, Lundell G, Nilsson B, Sjödin H, Lewin F, Lewensohn R. Long-term incidence of hypothyroidism after radiotherapy in patients with head-and-neck cancer. International Journal of Radiation Oncology*Biology*Physics. 2004 Oct 1;60(2):395–400.
11. Mercado G, Adelstein DJ, Saxton JP, Secic M, Larto MA, Lavertu P. Hypothyroidism A Frequent Event after Radiotherapy and after Radiotherapy with Chemotherapy for Patients with Head and Neck Carcinoma. Available from: https://onlinelibrary.wiley.com/terms-and-conditions
12. Akgun Z, Atasoy BM, Ozen Z, Yavuz D, Gulluoglu B, Sengoz M, et al. V30 as a predictor for radiation-induced hypothyroidism: A dosimetric analysis in patients who received radiotherapy to the neck. Radiation Oncology. 2014 May 2;9(1).
13. Kumpulainen EJ, Hirvikoski PP, Virtaniemi JA, Johansson RT, Èivi P, Simonen M, *et al*. Hypothyroidism after radiotherapy for laryngeal cancer [Internet]. Available from: www.elsevier.com/locate/radonline
14. Petersen K, Lindstedt G, Lundberg P -A, Bengtsson C, Lapidus L, Nyström E. Thyroid disease in middle-aged and elderly Swedish women: thyroid-related hormones, thyroid dysfunction and goitre in relation to age and smoking. J Intern Med. 1991;229(5):407–13.
15. Colevas AD, Read R, Thornhill J, Adak S, Tishler R, Busse P, et al. Hypothyroidism incidence after multimodality treatment for stage iii and iv squamous cell carcinomas of the head and neck. 2001.

ISSN (O): 2687-5365; ISSN (P): 2753-6556