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FUNCTIONAL HYPOTHYROIDISM IN PATIENTS RECEIVING CONCURRENT CHEMORADIATION FOR HEAD AND NECK SQUAMOUS CELL CARCINOMA.

Oncology/Radiotherapy

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ABSTRACT

Introduction: Head and neck cancers are the fifth most common globally and second most prevalent in India, with 77,000 annual cases. Radiotherapy, often combined with chemotherapy, is a standard treatment but frequently results in radiation-induced hypothyroidism (RIHT), with incidence rates ranging from 4% to 79%. RIHT significantly impacts quality of life, yet thyroid function testing is rarely routine. Hypothyroidism, a common late effect, is irreversible and requires lifelong hormone replacement. Preventive strategies are crucial to minimize this complication in patients undergoing radical radiotherapy with concurrent chemotherapy for head and neck squamous cell carcinoma. **Aim & Objectives:** This study examines the incidence of radiation-induced hypothyroidism in patients with HNSCC receiving chemoradiation and explores preventive strategies to reduce its occurrence and associated morbidity. **Materials and Methods:** This prospective study, conducted at GSL Medical College from October 2019 to April 2021, involved patients with head and neck squamous cell carcinoma receiving radical radiotherapy. Eligible patients underwent thyroid function tests before, after treatment, and six months post-radiotherapy. Dose-volume metrics were analyzed, and statistical assessments were performed using SPSS 22.0 and R version 3.2.2. Significance was set at $p < 0.05$. The study aimed to evaluate the incidence of radiation-induced hypothyroidism and explore preventive strategies. **Results:** In our study, 17 out of 31 patients (54.8%) developed radiation-induced hypothyroidism (RIHT) at 6 months post-radiotherapy, with 13 (41.9%) showing clinical hypothyroidism (mean TSH 7.77 ± 2.93, $p < 0.001$). T4 and T3 levels showed no significant difference between hypothyroid and euthyroid patients. Cold intolerance occurred in 12.9%, weight gain in 16.1%, dry skin in 29%, and constipation in 35.5% of patients. The mean thyroid dose was similar between hypothyroid (6570.29±587) and euthyroid groups (6541.35±601.13), with no statistically significant difference. Long-term follow-up is crucial, as RIHT incidence increases over time. **Conclusion:** Radiation-induced hypothyroidism (RIHT) is a common complication of head and neck radiotherapy, with our study reporting a 54.8% incidence at 6 months. While no clear dose-response relationship was identified, smaller thyroid volumes increased the risk of hypothyroidism. Early detection and long-term follow-up are essential to prevent progression from subclinical to clinical hypothyroidism. Further research is needed to improve predictive models and minimize thyroid exposure during treatment.

KEYWORDS

INTRODUCTION:

Head and neck cancers are the fifth most common globally and the second most prevalent in India, with 77,000 cases diagnosed annually[1]. Radiotherapy (RT) is a key treatment for locally advanced head and neck cancers, but combining RT with chemotherapy enhances outcomes by sensitizing cells to radiation and adding cytotoxic effects. The thyroid gland often falls within the radiation field, making thyroid hypofunction a common side effect. Hypothyroidism rates post-RT, alone or with surgery/chemotherapy, range from 4% to 79%. Symptoms like fatigue, dry skin, and cognitive issues severely impact quality of life, yet routine thyroid function testing in these patients remains uncommon[2-4]. Hypothyroidism (HT) is a common late effect of radiation, known as radiation-induced hypothyroidism (RIHT). Often overlooked during follow-up, RIHT causes systemic effects and is irreversible, requiring lifelong thyroid hormone replacement[5]. Levothyroxine generally reverses symptoms within weeks, though some neuromuscular and psychiatric effects may persist for months[6]. Therefore, efforts should be made to prevent or minimize hypothyroidism in patients undergoing radical radiotherapy with concurrent chemotherapy for HNSCC.

Aim And Objectives:

To study the incidence of radiation-induced functional hypothyroidism in patients receiving chemoradiation for HNSCC, evaluate the occurrence of hypothyroidism in euthyroid patients post-treatment, and assess preventive measures to reduce hypothyroidism and its associated morbidity in patients undergoing radical radiotherapy with concurrent chemotherapy.

MATERIAL AND METHODS:

This institutional-based prospective study was conducted at GSL Medical College and General Hospital from October 2019 to April 2021. It involved patients with histologically confirmed head and neck squamous cell carcinoma undergoing radical radiotherapy. Patients were immobilized from head to shoulders using a thermoplastic cast in the supine position with appropriate headrest. Contrast-enhanced planning CT images, with 3 mm slice thickness, were acquired from the supraorbital ridge to the carina. Following CT simulation, the images were transferred to the Treatment Planning System. Gross tumor volume (GTV) was delineated based on both clinical and radiological assessments. Clinical target volume (CTV), organs at risk (OAR), and planning target volume (PTV) were defined following standard guidelines. Eligible patients, aged 18 to 70 years with a Karnofsky Performance Status (KPS) score >70, received radical external beam radiotherapy using a Linear Accelerator Versa HD, delivering 66 Gy in conventional fractions with concurrent Cisplatin. Exclusion criteria included prior thyroid surgeries, nasopharyngeal cancer, primary thyroid malignancies, abnormal thyroid function tests, and stage IVc disease.

Thyroid function tests (T3, T4, TSH) were conducted before treatment, at the end of radiotherapy, and six months post-treatment, classifying patients as euthyroid or hypothyroid. The thyroid gland was contoured for analysis, and dose-volume metrics were calculated. Written consent was obtained, and patients were counseled on thyroid function tests. Follow-up assessments and data analysis were performed using SPSS 22.0 and R version 3.2.2, with descriptive statistics and chi-square tests for associations, setting significance at $p < 0.05$.

RESULTS:

In our study, TSH levels measured six months after radiotherapy showed a mean ± SD of 7.77 ± 2.93 (n=17) in hypothyroid patients versus 2.94 ± 1.28 (n=14) in euthyroid patients ($P < 0.001$, significant). T4 levels were similar, with a mean ± SD of 95.82 ± 38.26 in hypothyroid and 96.83 ± 38.5 in euthyroid patients (P not significant). T3 levels also showed no significant difference, with means of 2.93 ± 0.78 in hypothyroid and 1.7 ± 0.5 in euthyroid patients.

Cold intolerance was noted in 4 (12.9%) of 31 patients, with 2 hypothyroid and 2 euthyroid cases. Weight gain occurred in 5 (16.1%) patients, with 3 hypothyroid and 2 euthyroid cases. Constipation affected 11 (35.5%) patients, all of whom were hypothyroid. Dry skin was present in 9 (29%) patients, with 5 hypothyroid and 4 euthyroid. Although the mean maximum dosage was higher in the hypothyroid group, this difference was not statistically significant. Hypothyroid patients had the same mean dosage as euthyroid individuals, with no statistically significant difference.

Similarly, hypothyroid patients had a higher mean D95, but this difference was also not statistically significant.

TABLE –1 Thyroid Profile in Euthyroid Vs Hypothyroid Patients

PARAMETERS	EUTHYROID MEAN± SD	HYPOTHYROID MEAN ± SD	
TSH			
PRE-RT (n=31)	2.32±1.19 (n=31)	0	
END OF RT (n=31)	2.05±1.64 (n=31)	0	P<0.001
6 MONTHS POST RT (n=31)	2.94±1.28 (n=14)	7.77± 2.93 (n=17)	
T4			
PRE-RT (n=31)	98±34 (n=31)	0	
END OF RT (n=31)	99.9±54.6 (n=31)	0	P=0.943
6 MONTHS POST RT (n=31)	96.83±38.5 (n=14)	95.82± 38.26 (n=17)	
T3			P=0.354
PRE-RT (n=31)	1.7±1.0 (n=31)	0	
END OF RT (n=31)	1.7±1.6 (n=31)	0	
6 MONTHS POST RT (n=31)	1.7±0.5 (n=14)	2.93±0.78 (n=17)	

Table-2 Dose Vs TSH

PARAMETERS	TSH Hypothyroid n=17	Euthyroid n=14	P-VALUE
MAX DOSE			0.893
MEAN ± SD	6570.29±587.03	6541.35±601.13	
MEDIAN	6530	6580	
MIN-MAX	4645 -7139	4711 -7049	
INTERQUARTILE RANGE	6449 -7011	6520.25 -6972.75	
MEAN DOSE			0.940
MEAN ± SD	5916.23 ± 775.14	5934.42 ± 616.21	
MEDIAN	5779	5861.5	
MIN-MAX	4167- 6819	4240 - 6779	
INTERQUARTILE RANGE	5742- 6663	5743 - 6235	
D 95			0.713
MEAN ± SD	5533.52 ± 840.93	5425.64 ± 760.56	
MEDIAN	5580	5514.5	
MIN-MAX	3321 - 6682	3208 - 6638	
INTERQUARTILE RANGE	5310 - 6016	5221.25 – 5791.75	

Radiation-induced Hypothyroidism

Our study examined the incidence of hypothyroidism over six months. Radiation-induced hypothyroidism was observed in 17 out of 31 patients (54.8%). Among these, 4 patients (11.7%) had subclinical hypothyroidism, while 13 (41.9%) were clinically hypothyroid.

TABLE –3 INCIDENCE OF CLINICAL & SUBCLINICAL HYPOTHYROIDISM

OUTCOME (n=31)	PRE - RT	END OF RT	6 MONTHS POST-RT
NORMAL	31(100)	31(100)	14(45.1)
SUBCLINICAL	0	0	4(11.7)
CLINICAL	0	0	13(41.9)

DISCUSSION

The occurrence of radiation-induced hypothyroidism has been documented in publications since 1929[7]. Due to its location in the neck, the thyroid is often exposed to high radiation doses during head and neck cancer treatment. Hancock et al. reported that the relative risk of primary hypothyroidism decreases by 0.99 with each additional year of age[8].

Clinical hypothyroidism is characterized by elevated TSH, low T4, and symptoms like cold intolerance, weight gain, fatigue, dry skin, and constipation. Subclinical hypothyroidism involves elevated TSH with normal or low T4, often without symptoms. In our study, cold intolerance occurred in 12.9% of patients, weight gain in 16.1%, dry skin in 29%, and constipation in 35.5%, with most hypothyroid patients showing no symptoms.

Previous studies, such as those by Allan Carle and Gay J Canaris, reported that tiredness, dry skin, and shortness of breath were the most common symptoms in hypothyroidism. There was a positive association between symptom severity and TSH levels, supporting the use of symptoms to identify patients needing thyroid function tests[9-10].

Dose Vs Tsh

Several studies have explored the radiation dose and onset of radiation-induced hypothyroidism, but no definitive conclusions have been reached. Most report an incidence of 20-30%. While hypothyroidism has been noted after doses as low as 20 Gy, it is more frequently seen following doses of 30-45 Gy. Data on the correlation between total thyroid dosage and hypothyroidism remains conflicting. Posner et al.[11] contradicted Hancock[8] and Jereczek Fossa[12], who found a 1.02 relative risk increase per Gy of radiation.

In our analysis, the mean thyroid dose in hypothyroid and euthyroid groups was nearly identical (6570.29±587 vs 6541.35±601.13), showing no statistical significance. Several studies have examined the dose and timing of radiation-induced hypothyroidism (HT), but clear conclusions remain elusive. Most studies report an HT incidence of 20-30%. Hypothyroidism has been observed at doses as low as 20 Gy, though more commonly between 30-45 Gy. Posner et al. contradicted earlier studies that found a 1.02 relative risk increase per Gy[11].

In our study, the mean thyroid dose was similar between hypothyroid and euthyroid groups (5916.23 ± 775.14 vs 5934.42 ± 616.21), showing no significant difference. Thyroid dysfunction was seen at the lowest dose of 4804 cGy, with other studies showing a correlation between increased dose and thyroid dysfunction.

Boomsma et al. found that a higher mean thyroid dose increased the likelihood of HT, while a larger thyroid volume reduced it[13]. Similarly, Bhandare et al. noted a higher incidence of HT when the mean thyroid dose exceeded 45 Gy[14]. Other research has shown that smaller thyroid volumes are associated with a higher risk of HT, aligning with findings in our study where hypothyroidism was more prevalent in patients with smaller thyroid volumes.

IMRT without thyroid contouring has been associated with significant thyroid damage. Studies comparing IMRT and 3D conformal radiotherapy (3DCRT) found that IMRT, when the thyroid is not contoured, can result in higher doses to the thyroid and a greater risk of HT. Wu et al. reported that 3DCRT was linked to HT more frequently than conventional RT[15]. It is recommended to consider the thyroid as an organ at risk during IMRT planning and to minimize the thyroid dose. Various models have been proposed for predicting radiation-induced hypothyroidism, but none have gained widespread acceptance.

Clinical Correlation And Follow Up

In our study, the follow-up period was 6 months post-RT, shorter than in most studies. Srikantia et al. followed up for 9 months, Tell et al. for 3 years, and Turner et al. had a mean follow-up of 21 months. We found that 13 out of 31 patients (41.9%) developed clinical hypothyroidism at 6 months, a statistically significant result ($P < 0.00027$). No patients showed clinical hypothyroidism immediately post-RT, and 4 patients (11.7%) developed subclinical hypothyroidism, though this was not statistically significant.

Our incidence of 54.8% at 6 months is higher compared to other studies. Aich et al. found a 4.2% incidence at 12 months, while Srikantia et al. reported a 31.1% incidence. The literature reports an incidence range of 4-79%, with our study falling within this range. Research shows that subclinical hypothyroidism may progress to clinical hypothyroidism, and early diagnosis and treatment can prevent complications. Long-term follow-up is essential as the incidence of hypothyroidism increases with time, with most cases occurring within the first three years post-RT.

CONCLUSION

Radiation-induced hypothyroidism is a significant complication following head and neck radiotherapy, with our study demonstrating a higher incidence at 6 months (54.8%) compared to other studies. While no definitive correlation between radiation dose and hypothyroidism was established, smaller thyroid volumes were associated with increased risk. Early identification and management of hypothyroidism, alongside long-term follow-up, are critical to mitigate the progression from subclinical to clinical hypothyroidism and prevent potential complications. Further studies with longer follow-up are needed to refine predictive models and optimize radiation planning strategies to reduce thyroid exposure.

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