Original Article

# Hypothyroidism as a sequelae following treatment of head and neck cancer

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## Abstract

**Background:** Hypothyroidism is one of the late side effects seen after curative radiotherapy in the head and neck region encompassing part or whole of the thyroid gland. Still thyroid function tests are not a part of routine follow up of head – neck cancer patients treated with radiotherapy with or without surgery and / or chemotherapy. Aim of this study was to to find out the incidence of hypothyroidism in head – neck cancer patients treated with radiotherapy with or without chemotherapy and influence of concomitant chemotherapy. **Materials and Methods:** Of the 112 patients, 57 (50.8%) were planned to receive radiotherapy alone, 42 (37.5%) to receive neo-adjuvant chemotherapy with Cisplatin and 5-FU and the rest 13 (11.6%) patients to receive concurrent chemo-radiation. Thyroid function tests were done at the beginning of treatment, at six weeks after completion of radiotherapy and thereafter at six weeks' interval for two years. **Results:** After 24 months follow up, overall incidence of clinical hypothyroidism of our reported patients was 31.03% and of sub-clinical hypothyroidism was 37.93%. **Conclusion:** As a significant number of patients develop hypothyroidism following radiotherapy to the neck, thyroid function tests should be included in the routine follow up protocol of such patients.
**Keywords:** Hypothyroidism, head and neck cancer**,** radiotherapy, thyroid function tests.

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## INTRODUCTION

Hypothyroidism is the most common hormone deficiency. A depressed serum T4 level accompanying an elevated TSH level is recognized as a diagnostic of primary hypothyroidism. Hypothyroidism is characterized by underactive thyroid gland either due to the gland fails to produce enough T4 to meet the body's needs or the body fails to convert a sufficient amount of T4 to T3 in peripheral tissues, or the nervous system fails to stimulate the thyroid gland. This insufficient amount of hormone slows life-sustaining body processes, damages organs and tissues in the body, and can result in life-threatening complications. In developing countries, iodine deficiency remains an important cause of hypothyroidism.[1] Other common causes include destruction of the gland due to autoimmune disease or radiation; surgical removal of the thyroid; drugs and toxins; or infiltration of the tissue or rarely cancer.

Carcinoma of the head and neck region is the 5$^{th}$ most common malignancy worldwide[2] and commonest malignancy among Indian males, as per ICMR reports, probably due to increased use of chewing tobacco and smoking. Ionizing radiation to the neck is a known risk factor for the development of thyroid nodules, thyroid cancer, and primary hypothyroidism, particularly when exposure is during childhood. Hypothyroidism is one of the late side effects seen after curative radiotherapy in the head and neck region.

In the era of targeted therapies, many patients are on oral systemic therapy for cancer treatment. Additionally, some drugs used in the primary care setting have the potential to cause hormonal abnormalities. Targeted tyrosine kinase inhibitors (TKIs) are used in the treatment of renal cell cancers, pancreatic neuroendocrine

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tumors, hepatocellular carcinoma, and gastrointestinal stromal tumors. The TKIs can induce thyroid dysfunction, especially with sunitinib. Other TKIs associated with a variable risk of new-onset hypothyroidism include sorafenib, imatinib and nilotinib, etc.[3]

Low TSH levels with normal T4 and T3 levels in an asymptomatic patient are indicative of sub-clinical hyperthyroidism. Patients with head and neck cancers and/or history of radiation treatment to the pituitary region cannot be adequately assessed with only a TSH level, as a low TSH level due to decreased pituitary production can be misinterpreted as thyrotoxicosis. These patients may also have an inappropriately normal TSH level with frankly low levels of free T4 and would need medical therapy and ongoing monitoring of serum free T4 levels to monitor dosing. In this case, TSH deficiency is causing the low thyroid levels, and therefore both the TSH and free T4 levels are low.[4]

Because of both the nonspecific symptoms of hypothyroidism and the similar symptoms and morbidities associated with malignancies and their treatment, hypothyroidism can often go undiagnosed and untreated in patients with cancer. Failure to adequately manage both overt and subclinical hypothyroidism can have serious consequences, hence the recognition of its presence is crucial for the successful treatment of cancer patients.

The present study is an attempt to assess the radiation-induced sequelae on thyroid gland and long-term effects of concomitant chemotherapy.

## MATERIALS AND METHODS

In this prospective study, a total of 112 head and neck cancer patients diagnosed histologically and who were planned to receive therapeutic levels of radiation therapy to the head and neck region in which thyroid gland was included in the field of treatment. Patients with a prior history of thyroid disease or thyroid surgery, any neck surgery, abnormal pretreatment thyroid function tests and any previous history of radiation therapy to thyroid were excluded from the study. Patients having T4 tumors or N3 neck nodes or distal metastasis at presentation were also not included in the study because of their expected short survival.

Of the 112 patients, 57 (50.8%) were planned to receive radiotherapy alone, 42 (37.5%) to receive neo-adjuvant chemotherapy with Cisplatin and 5-FU and the rest 13 (11.6%) patients to receive concurrent chemo-radiation. In neo- adjuvant setting, Cisplatin was given in a dose of 50 mg/sq. meter per day on days 1 and 2 and 5-FU 600 mg/sq. meter per day by short infusion on days 1, 2 and 3. The cycle was repeated at 21 days interval for 3-4 cycles to be followed by external beam radiotherapy. In concurrent setting, Cisplatin 20 mg/sq. meter and 5-FU 300 mg/sq. meter were given weekly for five weeks along with radiotherapy, preferably on Fridays to give rest to the patients on weekends for recovery. All patients with or without completion of the proposed neo-adjuvant chemotherapy course, were treated with radiotherapy to the primary site as well as to the neck nodes covering the entire or most of the thyroid gland. Proposed dose of radiotherapy was 6000 – 6600 cGy in 30 to 33 fractions over a period of 40 to 45 days and was delivered by parallel opposing lateral beams with appropriate wedges with Tele-cobalt machine.

Before initiation of the treatment, all patients underwent complete physical examination and detailed history taking and physical examination, including thyroid gland, complete blood count, kidney function tests, liver function tests, X-ray chest, CT scan of the primary site and the neck. Thyroid function tests were repeated at six weeks after completion of radiation and thereafter at six months interval. Thyroid function tests were done by chemi-luminescence technique and the accepted normal values were T3: 60.0 – 181.0 ng/dl; T4: 4.5 – 12.6 μg/dl and TSH: 0.35 – 5.50 μIU/ml.

## RESULTS

Majority of the patients 68 (76.16) included in the study were in their sixth and seventh decade of life. Of the 112 patients, 57 patients received radiotherapy only, 42 received neo-adjuvant chemotherapy and the rest 13 patients received concurrent chemo-radiation. Of the 42 patients selected to receive neo-adjuvant chemotherapy, 26 patients completed the proposed four cycles, while 12 completed three cycles and the rest four patients discontinued after two cycles, mostly due to hematological toxicities and to some extent due to their unwillingness to continue further. Of the 13 patients planned to receive concurrent chemoradiation, eight completed the five cycles and in the rest chemotherapy was discontinued after three or four cycles mainly due to acute mucosal toxicities. Irrespective of chemotherapy cycles the patients have received, all of them have received external beam radiotherapy. 38 patients received 6600cGy, 56 received 6000cGy, 12 discontinued between 5000 – 6000cGy and the rest discontinued in between 4000 to 5000cGy.

All the selected patients were euthyroid at beginning of therapy but the incidence of hypothyroidism increased with the passage of time. The time period was calculated from the date of completion of radiotherapy. After 24 months follow up, overall incidence of clinical hypothyroidism of our reported patients was 31.03% and of sub-clinical hypothyroidism was 37.93% (Table 1).

**Table 1:** Incidence of hypothyroidism with long term follow up

| Post RT Time period | No. of patients attended follow up | | | Clinical hypothyroidism | | | Sub-clinical hypothyroidism | | |
|---|---|---|---|---|---|---|---|---|---|
| | RT | NRT | CRT | RT | NRT | CRT | RT | NRT | CRT |
| 6 weeks | 53 | 40 | 13 | 0 | 0 | 0 | 0 | 0 | 1 |
| 6 months | 50 | 38 | 12 | 0 | 0 | 1 | 2 | 2 | 1 |
| 12 months | 45 | 33 | 11 | 3 | 2 | 2 | 4 | 4 | 2 |
| 18 months | 38 | 29 | 8 | 6 | 6 | 2 | 7 | 8 | 3 |
| 24 months | 30 | 24 | 4 | 8 | 7 | 3 | 10 | 9 | 3 |

**RT:** External beam radiotherapy
**NRT:** Neo-adjuvant chemotherapy and radiotherapy
**CRT:** Concomitant chemotherapy and radiotherapy

## DISCUSSION

There is a general agreement that hypothyroidism is a much more common complication following combined surgical and radio-therapeutic management of head and neck cancers. The exact reason about hypothyroidism sequelae after radiotherapy is incompletely understood. This may be due to direct follicular destruction or prevention of cell division or vascular damage to the thyroid gland or immunologically mediated damage to the thyroid gland or a various combination of the factors. Histological examination of the thyroid gland after external irradiation has documented follicular cell damage and vascular damage following doses as low as 225 cGy.[5] An immunologic influence has been suggested by Einhorn and Wikholm.[6]

Incidence of hypothyroidism following combined surgical and radio-therapeutic management of head and neck cancers ranges in literature from 43 to 66 % often depending upon the duration of follow up.[7-9] On the other hand, some researchers have claimed that hypothyroidism is a rare or nonexistent complication of radiotherapy alone to the neck.[10]

After 24 months follow up, overall incidence of clinical hypothyroidism of our reported patients was 31.03% and of sub-clinical hypothyroidism was 37.93%. Due to diversity of reported incidences, type of managements and duration of follow up in published series, it is almost impossible to compare our results with others. Mercado *et al* reported 48% and 67% Kaplan – Meier projected incidence of hypothyroidism at 5 and 8 years respectively with a median follow up of 4.4 years, when patients with head and neck malignancies were treated with external beam radiotherapy with or without concurrent chemotherapy.[11] The median time to the development of hypothyroidism was 1.4 years. Turner *et al* reported 14.3% incidence of clinical and 23.8% sub-clinical hypothyroidism following radiotherapy to the whole of the thyroid gland. They estimated that by 5 years up to 40% of the patients may become hypothyroid. In their study, 6 % patients developed clinical and 22 % sub-clinical hypothyroidism at a median follow up of 19 months. Median time to develop hypothyroidism was 15 months. In their series, incidence of sub-clinical hypothyroidism was significantly higher when whole of the thyroid gland was included in the target volume compared to patients where only part of the thyroid gland was irradiated.[5] The results are consistent with the present study. No effect of age, sex, primary site, neck node status or radiation dose on the incidence of hypothyroidism observed in the present study. Similar were the findings of Mercado and Tell.[11,12]

The importance of making the diagnosis of hypothyroidism in these patients lies in the fact that treatment with thyroid hormone replacement is simple, inexpensive, and effective and usually without major side effects especially in <45 years age group.

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