Original Article

# Head and neck radiotherapy - A risk factor for anaesthesia?

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## ABSTRACT

**Background:** The aim was to study perioperative management in head and neck cancer, the commonest cancer in Indian men, after radiation therapy. Radiotherapy (RT) targets the tumour and the neck including the thyroid gland. RT induced physical effects (on the airway) and physiological effects (on the thyroid) impact perioperative care. Patients with RT-induced subclinical and mild clinical hypothyroidism are often asymptomatic. Cancer surgery is time-sensitive. Given that parenteral levothyroxine is not available, is a TSH of 15 acceptable for cancer surgery? **Methods:** A retrospective study was conducted in a tertiary cancer centre. The records of elective surgery (72 patients) were scrutinised. Data on thyroid profile, airway, treatment of clinical and subclinical hypothyroidism, airway access, recovery and perioperative haemodynamic parameters were retrieved. Correlation of age, sex, RT, chemotherapy with hypothyroidism was done by Chi-square test. The perioperative course was studied. **Results:** Hypothyroidism (subclinical and clinical) was diagnosed in 39% of patients. All were asymptomatic. There was a significant association between RT and hypothyroidism. In 50% of patients, we encountered a difficult airway. In subclinical hypothyroidism (TSH less than 15), after levothyroxine initiation, the course of anaesthesia, extubation, recovery and postoperative stay was uneventful. **Conclusions:** Hypothyroidism and difficult airways are a common sequel of RT. Selected cancer patients with subclinical hypothyroidism had a smooth perioperative course.

**Key words:** Airway, head and neck cancer, radiotherapy, subclinical hypothyroidism

## INTRODUCTION

Head and neck cancer (HNC) is the commonest cancer in Indian men.[1] Radiotherapy (RT) targets the primary tumour and the neck including the thyroid gland in the field. Radiation-induced physical effects (on the airway) and physiological effects (on the thyroid) have an impact on perioperative care.

The incidence of radiation-induced hypothyroidism in HNC patients is reported to be 23–53% as compared to 3–8% in normal subjects,[2-4] patients are often asymptomatic and hypothyroidism remains undetected.[2]

Anaesthesia in the hypothyroid patient is associated with significant risks. Cancer surgery is time-sensitive. Strict recommendations for correction to the euthyroid status before elective major surgery may, therefore, need to be revisited. The dilemma arises when cancer surgery is scheduled in a patient with biochemical hypothyroidism or mild hypothyroidism. The thyroid-stimulating hormone (TSH) level at which cancer surgery and anaesthesia are safe is not defined. Can a TSH of 15 be considered safe in the asymptomatic patient? This is, especially relevant because parenteral thyroxine supplements are not available to us.

The risks associated with hypothyroidism need to be weighed against the urgency of surgery.



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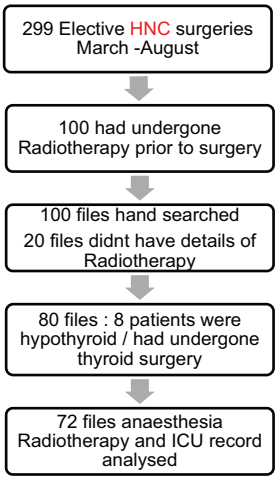
Radiation induced airway changes have been researched less. RT may increase the difficulty in mask holding and intubation owing to short-term (vocal cord oedema, mucositis, glossitis) and long-term effects (fibrosis, trismus, decreased mobility of the tongue and neck, loss of teeth and osteoradionecrosis).[5,6]

There is a dearth of evidence in the anaesthesia literature on this patient population. The aim was to study perioperative care of post-RT HNC patients. The primary objective was to learn about the burden of asymptomatic post-RT hypothyroidism at the anaesthesia clinic. The secondary objective was to asses the safety of anaesthesia. The impact of RT on airway was also explored. Research in this field has a major impact on clinical practice and patient outcomes because a large number of patients undergo surgery after RT.

## METHODS

The institutional review board and ethics committee (BMH/2019/1199) dated 8th June 2019) approved of a retrospective study on patients of HNC who had undergone elective surgery after RT. [See flow chart].




Data were analysed from the files of 72 patients. As per institutional protocol all these patients had their thyroid functions (TFTs) evaluated. Patients who had received chemotherapy (CT) were included.

The sample size was calculated at a 95% confidence interval and 10% allowable error using the formula for the sample size for estimation of a single sample proportion. The sample size was calculated to be 77. This was based on the expected proportion of RT induced hypothyroidism as 26%[7] and standard normal deviate for 95% confidence limits as 1.96.

Age, sex, diagnosis, CT, details of RT and TFTs were collected from the records. Subclinical hypothyroidism was defined as raised TSH levels (TSH more than 5.5 micro IU/mL) with normal T3, T4 levels and clinical hypothyroidism as raised TSH and low T3, T4 level.[8] The endocrinologist started levothyroxine for all patients with hypothyroidism. Patients of subclinical hypothyroidism were taken up for surgery with a TSH cut-off value of 15 IU as per institutional protocol.[9] In clinical hypothyroidism, surgery was postponed till free T3 and T4 were normal.

The airway was assessed by LEMON Score (look, evaluate, Mallampati, obstruction and neck mobility).[10] The sternomental distance of less than 12.5 cm was used to assess the limitation of neck mobility and head extension.[10] A difficult airway was anticipated in 40% of patients. As a protocol, all anticipated difficult airways are intubated awake using a flexible bronchoscope. The primary technique in other patients is direct laryngoscopy. If intubation is not possible after two more attempts, changed blades, position and anaesthesiologist, asleep intubation with flexible bronchoscope is used. The need for fibreoptic intubation and multiple manoeuvres for intubation was considered 'difficult intubation'.

## RESULTS

Table 1 displays demographic data [Table 1]. Hypothyroidism was diagnosed in 39% of patients who had received RT for non-thyroid HNC. Hypothyroidism was more common in patients with carcinoma tongue. Of the patients who received RT alone, 52% developed hypothyroidism as compared to 31% in the group that received both RT and CT. [Figure 1 and 2] Around 39% had clinical hypothyroidism and 61% subclinical hypothyroidism [Figure 1]. None of the

**Table 1: Demographic data**

| | No. of Patients |
|---|---|
| Age | |
| <20 years | 0 |
| 20-40 years | 10 (13.8%) |
| 41-60 years | 42 (58.3%) |
| 61-80 | 21 |
| Sex | |
| Male | 63 (83%) |
| Female | 10 (17%) |

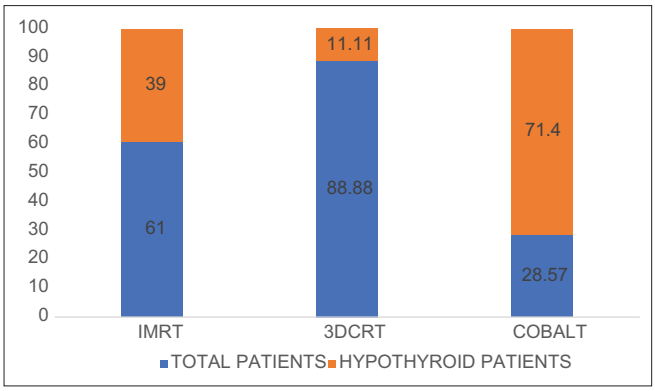



**Figure 1:** Modality of RT and hypothyroidism

patients had dry skin, slow mentation, weight gain, cold intolerance, depression, lethargy or symptoms of coronary artery disease (CAD).

The interval between RT and deranged TFTs ranged between 3 months to 16 years. Around 77% of patients underwent intvensity-modulated radiation therapy (IMRT) while 12% received 3D conformal RT (CRT) and 11% received cobalt therapy. Hypothyroidism was more common in patients after cobalt therapy (71%).

About 40% of patients had trismus and a rigid neck with limited extension.

All the patients had a normal electrocardiogram (ECG) and echocardiography.

Nearly 55% of patients had difficult intubation (anticipated and unanticipated difficult airway). Direct laryngoscopy was difficult due to, decreased mobility of tongue and difficulty in lifting the epiglottis. Despite a comprehensive assessment, a difficult airway had not been predicted in 10% of patients.

The surgery duration varied from 2 h to 8 h. No patient had a delayed recovery, hypothermia, prolonged response to neuromuscular blockade or intraoperative hypotension. None of the patients had unexplained hypotension or hyponatremia. The perioperative course of all was uneventful except two (corrected hypothyroid) patients who developed intraoperative atrial fibrillation.

The statistical analysis (Chi-square test) revealed a positive correlation between RT and hypothyroidism. ($P < 0.05$). There was no association of age, gender and CT with hypothyroidism.

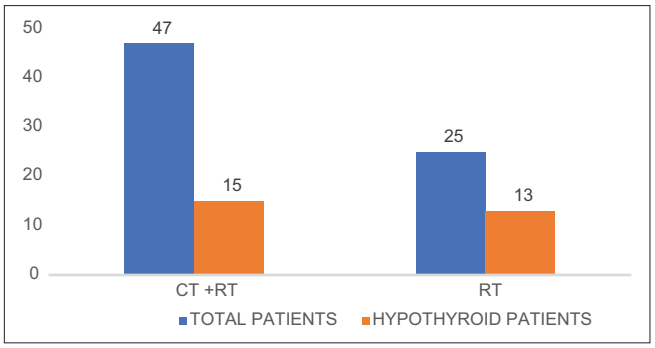



**Figure 2 :** CT, RT and hypothyroidism

## DISCUSSION

The sequelae of head and neck RT include thyroid-related morbidity and airway changes.

RT-induced hypothyroidism is often undetected. Despite advances in RT, the common late effect is hypothyroidism. This may be overt (clinical hypothyroidism- low free T4 and high TSH), or subclinical (compensated - normal free T4 and high TSH). In most cases, subclinical hypothyroidism progresses to clinical hypothyroidism.[11] Development of clinical hypothyroidism occurs at a rate of about 5 to 20% per year.[12] Clinical hypothyroidism typically manifests by slow mentation, depression, dry skin, pleural and pericardial effusions, decreased gastrointestinal motility, weight gain, cold intolerance, chronic fatigue, congestive heart failure, decreased wound healing and acceleration of atherosclerosis.[9] None of our patients had any of these symptoms. However, 39% of our patients had hypothyroidism.

In a similar study, hypothyroidism was reported to be 48% over a median follow-up of 5 years.[13] Incidence of hypothyroidism was high with IMRT in a previous study.[11] RT may cause hypothyroidism in months to years. Aich *et al.* evaluated the thyroid status after 6-weeks.[3] They noticed a 4.2% incidence of clinical hypothyroidism at 12 months and not earlier. In our study, the longest follow-up was 16 years and the shortest was 3 months.

Srikantia *et al.* found that[12] 52.9% of the patients developing clinical hypothyroidism were 51 to 60 years old. ($P = 0.0522$); however, the mean patient age analysed were in the range of 52 years. The higher occurrence among female patients (50%, F: M = 1.5: 1) was not statistically significant. There was no correlation between hypothyroidism with age or gender in our study. Hypothyroidism was not

associated with CT which was supported by many studies.[13-15]

Guidelines recommending TFTs during routine follow-up after RT[16] are not followed strictly. Subclinical and asymptomatic thyroid dysfunction may be missed.

Hypothyroidism affects the response to anaesthesia. Consequences of subclinical hypothyroidism include cardiac dysfunction, atherosclerotic disease and cardiovascular mortality and progression to clinical hypothyroidism.[16-18] Sudha *et al.* reported an intraoperative cardiac arrest in a cancer patient with undetected hypothyroidism.[18] Two of our patients had very high TSH values of TSH (95,179 IU). Non-specific symptoms of lethargy and fatigue in hypothyroidism may be attributed to cancer and therapy leading to underdiagnosis. Apathy associated with hypothyroidism may itself contribute to late diagnosis.[9] There is evidence of early post-RT thyroiditis and hyperthyroidism from Iran.[19] Alterio *et al*. also emphasised that, of radiation-induced late effects, thyroid disorders are underestimated.[20]

Eltroxin replacement improves cardiac function in subjects with subclinical hypothyroidism.[8] It is important to recognise subclinical hypothyroidism early and prevent clinical hypothyroidism.[8] In aortic valve surgery, there are increased chances of postoperative atrial fibrillation in patients of subclinical hypothyroidism.[21]

Hypothyroidism is usually corrected before elective surgery. There is a dilemma when the surgery is time sensitive as in cancer and the patient has biochemical hypothyroidism. This is especially relevant because parenteral thyroxine is not available. There is no consensus about scheduling cancer surgery in mild or moderate hypothyroidism.[22] After non-cardiac surgery in euthyroid, treated hypothyroidism (TSH less than 5.5) and mild hypothyroidism (median TSH 8.6), Komatsu *et al.*[23] observed that hypothyroid patients received more vasopressors and were discharged later. But there were no significant differences in the primary composite outcome i.e., hospital cardiovascular morbidity, surgical wound complication or infection. They concluded that postponement for thyroid replacement seemed unnecessary. In our patients with clinical hypothyroidism, surgery was deferred till the free T3, T4 levels came to normal. The perioperative course of all the subjects was uneventful except two patients (euthyroid at the time of surgery) who developed intraoperative atrial fibrillation.

Weinberg *et al*.[24] reported that there were no significant differences in duration of surgery or anaesthesia, arrhythmias, lowest temperature, blood pressure, time to extubation, vasopressor support, fluid and electrolyte imbalance, sepsis, myocardial infarction, pulmonary and bleeding complications, or time to discharge in 59 hypothyroid compared with 50 euthyroid patients. They concluded that there was no evidence to postpone surgery until the correction of mild or moderate hypothyroidism. Drucker and Burrow[25] also reported the safety of anaesthesia after major cardiovascular surgery in mild-to-moderate hypothyroidism without levothyroxine supplementation.

The benefits of treatment of subclinical hypothyroidism against the potential risks have been evaluated by many. It is of value in symptomatic patients and before major surgeries, it may, however, increase the risk because of possible angina. The critical question is the safe cut-off value of TSH at which surgery is permissible. According to Mythen and Fleischer, TSH values of 5 to 15 mU/L (range 0.3 to 4.5 mU/L) may have 'little or no perioperative significance'.[9]

All our patients of subclinical hypothyroidism were taken up for surgery with a TSH less than 15 IU after starting levothyroxine.[8] None of our subjects had coronary artery disease (CAD).[8] The perioperative course of all was uneventful.

Anaesthesia in hypothyroid patients in emergency surgery poses problems. In symptomatic CAD, the need for thyroxine must be balanced against the risk of aggravating angina. Levine suggested early consideration of coronary artery bypass grafting (CABG).[26] However, deaths from arrhythmia and congestive heart failure, cardiogenic shock with infarction, have occurred in patients who were not given thyroxine and were waiting for surgery. Therefore, he recommended that true emergency CABG should be considered in patients with both severe CAD and significant hypothyroidism. He advocated postoperative thyroxine in the ICU. A recent review[27] also recommended that patients with mild or moderate hypothyroidism may proceed for urgent or emergent surgery with caution. Mahmoud *et al*.[28] studied subclinical hypothyroid patients (TSH 7–11 mU/L) undergoing elective off-pump CABG. Group A was given three doses of Eltroxin in 48 h

before surgery. (Group B patients - placebo). Patients in both groups were administered Eltroxin from the first postoperative day (100 mcg on day 1 followed by 50 mcg per day). Patients in both groups had significant myocardial depression compared with preoperative value and an increased incidence of supraventricular arrhythmias, mainly atrial fibrillation. They found an increased incidence of operative and postoperative complications in Group B.

It would appear from the above studies that urgent surgery in subclinical hypothyroidism (up to TSH 15) are a special subset of patients. In an asymptomatic patient, the urgency of surgery takes priority and it may be undertaken with due precautions throughout the perioperative course.

In our study, difficult intubation was seen in 50% of patients. Chronic sequelae of radiation to neck include temporomandibular joint fibrosis and non-compliant neck tissues. The resulting trismus and woody neck[6] impede mask ventilation and laryngoscopy.[29] [Table 2]. Subtle changes to voice, dysphagia, orthopnoea and new onset of snoring may be a sign of airway compromise.

In slowly progressing cancer, with the conditioning of the respiratory muscles, patients may have relatively few signs or symptoms, despite significant narrowing. Radiation fibrosis syndrome is a combination of tonic contraction and fibrosis of the muscles of mastication.[30] RT induced trismus and limited neck range of motion do not improve with anaesthetic induction or a muscle relaxant, unlike trismus due to pain or inflammation.

In a similar study.[30] 22.3% of patients treated with RT had restricted neck movement (compared to 11.0% of non-RT patients). More patients in the RT group had trismus (24.8% versus 18.7%). Nusrath[29] emphasised the need for an 'airway management strategy' in HNC.

The perioperative course may also be impacted by RT-induced baroreceptor damage, carotid artery stenosis and poor wound healing.[29]

Most studies on thyroid disorders after RT are retrospective and are on a heterogeneous/small patient population. Though our study is retrospective, it was specifically focussed on the impact of RT on the anaesthetic considerations in non-thyroid HNC. Larger prospective studies are needed to define the time frame of radiation-induced hypothyroidism. The safety of anaesthesia in clinical and subclinical hypothyroidism in semi-elective surgery also needs to be studied in larger populations. The safe level of TSH needs to be defined.

There is some literature on elective and emergent CABG in subclinical and overt hypothyroidism. To our knowledge, this is the first study on cancer surgery in subclinical hypothyroidism.

Head and neck RT is a risk factor in anaesthesia for HNC surgery and needs to be factored in the preoperative optimisation. This is not part of routine anaesthesia risk stratification.

This study has some limitations. This is a retrospective study. So, some patients may have been hypothyroid (asymptomatic, undiagnosed) before RT. It is also difficult to comment on the latent period for hypothyroidism to manifest after RT from our study.

**Table 2: Airway changes after radiotherapy (modified from Balakrishnan *et al*.[6])**

| Site | Pathology | Change | | Anaesthesia implication |
|---|---|---|---|---|
| | | Early | Late | |
| Face and buccal mucosa | Necrosis, mucositis | Oral candidiasis, pain | Ulcers<br>fistula | Difficult mask ventilation, bleeding |
| TM joint | Fibrosis | | Trismus | Difficult laryngoscopy and intubation |
| Tongue | Fibrosis, inflammation | Glossitis | Tongue oedema, large tongue, mobility, ankyloglossia | Falsely raises the grade of Mallampati, difficulty laryngoscopy |
| Dentition | Increased risk of caries | Increased mobility | Loss of teeth | Difficult in mask ventilation, dislodgment of teeth |
| Floor of mouth | Fibrosis | | Fixity of tongue, ankyloglossia | Difficult laryngoscopy |
| Mandible | Osteonecrosis or osteomyelitis, fracture | Asymptomatic dehiscence of the mucosa | Micrognathia/<br>mandibular recession<br>Extraoral/intraoral fistulae | Reduction in mandibular space, difficult mask ventilation |
| Suprahyoid region | Fibrosis oedema | | The pliability of neck tissue decreases, firm/woody neck, skin tethered, | Neck rigidity, Limited flexion and extension at the atlantooccipital joint, decreased sternomental distance |
| Lower airway | Glottic oedema, epiglottis oedema | | Snoring, hoarse voice, | Difficult intubation, inadequate visualisation of the larynx |

The cancer, prior surgery and/or RT will all contribute to a difficult airway.[31] It is, therefore, difficult to define the impact of RT alone. Besides, the intubation technique used depends on local practice, indications and the personal preference and skills and experience[31] of the provider. In this study, all the intubations were performed by HNC anaesthesiologists who routinely use flexible bronchoscopy. The results of this study might not apply to providers with different skill sets and instruments.

## CONCLUSION

Surgery after head and neck RT poses a set of challenges for the anaesthesiologist. Evaluation for hypothyroidism must be done, as patients are often asymptomatic. An airway management strategy is needed as RT may compound the tumour related difficulty in airway access. In carefully selected asymptomatic patients with subclinical hypothyroidism, a TSH value of 15 is safe (in consultation with the endocrinologist) for the conduct of anaesthesia in time-sensitive HNC surgery.

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### Conflicts of interest

There are no conflicts of interest.

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