Research Article

A prospective study of radiation-induced hypothyroidism in head and neck cancer patients

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ABSTRACT

Background: Head and neck cancers are one of the most common cancers worldwide. Radiotherapy is the only curative treatment, besides surgery. The most common clinical late effect of thyroid gland irradiation in patients exposed to therapeutic doses to the neck is hypothyroidism, and hypothyroidism causes morbidity and mortality if untreated. There is not enough data about post-radiotherapy hypothyroidism in head and neck cancer patients in eastern India. **Objectives:** The purpose of our study is to identify the incidence of hypothyroidism following radiotherapy in head and neck cancer patients in eastern India and to assess the time period for the development of hypothyroidism for early treatment to reduce hypothyroid related morbidity and mortality. **Materials and Methods:** The study was done in 107 histopathologically proved head and neck cancer patients between June 2013 and May 2016. Patients were treated with Cobalt 60 Teletherapy machine with conventional fractionation. 31 (28.9%) patients received concurrent chemoradiation with weekly Cisplatin, 50 (46.7%) patients received radiation alone, and 26 (24.3%) patients received neo-adjuvant chemotherapy with injection Paclitaxel and injection Carboplatin followed by radiation. **Results:** Male patients were 80 (74.8%) and 27 (25.2 %) were female patients, and the age groups were 42–70 years, and the median age was 52 years. Primary tumor in the majority of the patients was carcinoma larynx 51 (47.6%). At 36 months of follow-up 13 (25%), patients were to have subclinical hypothyroidism, 9 (17.3%) patients were to have clinical hypothyroidism, and percentage of hypothyroidism was 42.3%. The first occurrence of hypothyroidism was seen over a follow-up period of 6 months in our study. **Conclusion:** It is recommended that serum thyroid stimulating hormone and free T4 have been estimated before initiation of radiotherapy and post radiotherapy at regular interval 6–12 months and carried out lifelong and physicians should not neglect to evaluate thyroid function of post-radiotherapy head and neck cancer patients.

KEY WORDS: Head and Neck Cancer; Radiotherapy; Hypothyroidism

INTRODUCTION

Head-neck cancers affect the upper aerodigestive tract and are one of the most common cancers worldwide.[1] Head-neck cancers are the second most common cancers in the Indian population and 77,000 cases diagnosed per year.[2] While smoked tobacco and alcohol are the major causative factors for head-neck cancers worldwide, smokeless tobacco, betel nut, and Epstein–Barr virus are etiological agents responsible for it in the Asian population.[3] The management of head-neck cancer requires a multimodality concept and multidisciplinary approach which include radiotherapy, chemotherapy, surgery, and a combination of these. In the management of head-neck cancer patients, radiotherapy is the one of the most important curative approaches, besides surgery. Majority of head-neck cancers are loco-regionally advanced at the time

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of diagnosis. Hence, the radiotherapy treatment field covers the primary site of the tumor and whole neck including the thyroid gland. The thyroid gland is situated in an anterior part of the neck in front of the trachea and secretes the principal hormones thyroxine (T4) and triiodothyronine. The thyroid gland maintains the level of metabolism in the tissues that is optimal for their normal functioning. Hypothyroidism is the most common clinical delayed effect of post-radiotherapy head-neck cancer patients. Hypothyroidism may be clinical and subclinical. Clinical hypothyroidism is characterized by low free T4 and high thyroid stimulating hormone (TSH), and subclinical hypothyroidism is characterized by normal free T4 and high TSH. Subclinical hypothyroidism is also called compensated hypothyroidism. In the majority of cases, subclinical hypothyroidism progresses to clinical hypothyroidism.[4] The mechanism of radiation-induced hypothyroidism is that radiation causes both microvascular and macrovascular damage, directly, in and around the thyroid gland and it causes tissue hypoxemia and nutrient-poor environment causes in a reduced synthetic and secretory capacity of the gland itself. Radiofibrosis of the gland's capsule may also inhibit compensatory hypertrophy in this situation. Progression to clinical hypothyroidism occurs at a rate of about 5–20% per year. Symptoms of hypothyroidism are weakness and fatigue, dry skin, feeling cold, hair loss, difficulty in concentrating and poor memory, neuropsychiatry disorder, weight gain despite poor appetite, pleural and pericardial effusion, and atherosclerosis. Early diagnosis and proper treatment reduce the rate of morbidity and mortality.

Hypothyroidism after radiotherapy alone or in combination with surgery and/or chemotherapy for patients with head-neck cancers has been well reported between 17% and 51% in the literature.[5-8] Routine assessment of thyroid function of post-radiotherapy head-neck cancer patients is not done during follow-up. Hence, post-radiotherapy hypothyroidism is remained unrecognized and underreported resulting in failure to treat morbidity of hypothyroidism for a significant proportion of surviving patients.

Study on post-radiotherapy hypothyroidism in head-neck cancer patients is mostly retrospective, lack of post-radiotherapy evaluation, small number of patients and is short period of follow-up. There is not enough data about post-radiotherapy hypothyroidism in head-neck cancer patients in Eastern India. Hence, the purpose of our study is to identify the incidence of hypothyroidism following radiotherapy in head-neck cancer patients and to assess the time period for the development of hypothyroidism for early treatment to reduce hypothyroid related morbidity and mortality.

MATERIALS AND METHODS

The study was done with 107 patients at the Department of Radiotherapy, N.R.S Medical College, Kolkata, between June 2013 and May 2016. Histopathologically proved head and neck cancer patients having pre-radiotherapy normal range TSH and free T4 level were included in the study. The previous history of radiotherapy in neck, neck and thyroid surgery, and chemotherapy was excluded from this study. The patients with thyroid gland infiltration (T4) by primary tumor and N3 disease were excluded from our study. Patients were treated with Cobalt 60 Teletherapy machine with dose per fraction 2 Gy, and treatment was given 5 days in a week. The treatment portals were two lateral parallel oppose fields included the primary tumor with margin and the whole neck. The primary and the gross nodes were treated up to 66 Gy and after 44 Gy fields were reduced to spare the spinal cord. Few patients received concurrent chemoradiation with weekly Cisplatin at 40 mg/m^2 of body surface area, and few patients received neo-adjuvant chemotherapy with injection Paclitaxel 175 mg/m^2, injection Carboplatin AUC 5 2–3 cycles followed by radiation. Serum TSH and free T4 were estimated at 1 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months following completion of external beam radiotherapy. The normal values used for our study were TSH 0.5–4.7 μU/ml and free T4 0.8–2.7 ng/dl.

RESULTS

In our study, total number of patients was 107. Male patients were 80 (74.8%) and 27 (25.2 %) were female patients, and the age groups were 42–70 years, and the median age was 52 years. Primary tumor in majority of the patients was carcinoma larynx 51 (47.6%), other sites of primary tumor were oropharynx 29 (27.1%), hypo-pharynx 16 (14.9%), oral cavity 9 (8.4%), and nasopharynx 2 (2%) [Table 1]. 50 (46.7%) patients received radiation alone, 31 (28.9 %) patients received concurrent chemotherapy with cisplatin, and 26 (24.3%) patients received neo-adjuvant chemotherapy with injection Paclitaxel 175mg/m^2 and injection Carboplatin AUC 5 2–3 cycles followed by radiation.

In our study, clinical and subclinical hypothyroidism was studied after completion of external beam radiotherapy at 1 month, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months. At 36 months after completion of radiotherapy, 13 (25%) patients were to have subclinical hypothyroidism, 9 (17.3%) patients were to have clinical hypothyroidism [Table 2], and percentage of hypothyroidism was 42.3%. The first occurrence of hypothyroidism was seen at 6 months of post-radiotherapy in our study. At 36 months of follow-up among male patients, 16 (20%) of 80 and among female patients, 6 (22.2%) of 27 developed hypothyroidism, and 5 (9.6%) patients in only radiotherapy group developed hypothyroidism, 10 (19.2%) patients in concurrent chemoradiation group developed hypothyroidism, and 7 (13.4%) patients in neo-adjuvant chemotherapy followed by radiotherapy group developed hypothyroidism [Table 3]. There was no effect of age, primary site on the incidence of hypothyroidism in our study. All clinical or subclinical

Table 1: Patients characteristics (*n*=107)

Characteristics	Value (%)
Age	
Range	42-70 years
Median age	52 years
Gender	
Male	80 (74.80)
Female	27 (25.20)
Primary disease Sites	
Larynx	51 (47.60)
Oropharynx	29 (27.10)
Hypopharynx	16 (14.90)
Oral Cavity	9 (8.40)
Nasopharynx	2 (2.00)
Stage of the disease	
I	20 (18.70)
II	56 (52.30)
III	31 (29.00)

Table 2: Incidence of hypothyroidism during follow-up

Post RT time period	Hypothyroidism	
	Subclinical (%)	Clinical (%)
1 Month (*n*=107)	0	0
6 Months (*n*=107)	2 (1.8)	0
12 Months (*n*=105)	5 (4.76)	2 (1.8)
18 Months (*n*=98)	9 (9.2)	4 (4.0)
24 Months (*n*=85)	11 (12.9)	5 (5.8)
30 Months (*n*=69)	11 (15.9)	6 (8.6)
36 Months (*n*=52)	13 (25)	9 (17.3)

Table 3: Occurrence of hypothyroidism at 36 months

Total patients	RT alone	Concurrent CT-RT	NACT→RT
(13+9)=22	5 (9.6)	10 (19.2)	7 (13.4)

hypothyroid patients were checked up by the endocrinologist, and thyroid supplementation was given.

DISCUSSION

The study was done in 107 patients at the Department of Radiotherapy, N.R.S Medical College, Kolkata, between June 2013 and May 2016. Male patients were 80 (74.8%) and 27 (25.2 %) were female patients, and the age groups were 42–70 years, and the median age was 52 years. Primary tumor in majority of the patients was carcinoma larynx 51 (47.6%). At 36 months of follow-up 13 (25%), patients were to have subclinical hypothyroidism, 9 (17.3%) patients were to have clinical hypothyroidism, and percentage of hypothyroidism was 42.3%. The first occurrence of hypothyroidism was seen at 6 months in our study. At 36 months of follow-up among male patients, 16 (20%) of 80 and among female patients, 6 (22.2%) of 27 developed hypothyroidism, and 5 (9.6%) patients in only radiotherapy group developed hypothyroidism, 10 (19.2%) patients in concurrent chemoradiation group developed hypothyroidism, and 7 (13.4%) patients in neo-adjuvant chemotherapy followed by radiotherapy group developed hypothyroidism.

Radiotherapy is one of the curative treatment approaches in the treatment of head-neck cancer patients, which can be administered alone, or with surgery or with chemotherapy. Hypothyroidism is the most common and delayed clinical effect of post-radiotherapy head-neck cancer patients. In 1961, Felix *et al*. first reported a case of hypothyroidism six years after treatment of laryngeal carcinoma with external radiotherapy in a patient.[9] The causes of post-radiotherapy hypothyroidism are parenchymal cell and vascular injury of the thyroid gland, and also autoimmune reactions.[10,11] Alterio *et al*. reported that primary hypothyroidism was the most frequent late effect in post-radiotherapy head-neck cancer patients and incidence was 20%–30%.[12]

In our study, the age range of patients was 42–70 years with a median age was 52 years. 80 (74.8%) patients were males and 27 (25.2%) patients were females. Majority of the primary site of cancer was laryngeal cancer (47.6%). There is a variation of the primary site in literature. In a study of Aich *et al*., a higher percentage of cancers were originated from the larynx (49%).[13] As all the patients received whole-neck irradiation and hence uniformity in the volume of thyroid irradiated the primary site of the tumor was not a significant factor.

In our study at 36 months of follow-up 13 (25%), patients were to have subclinical hypothyroidism, 9 (17.3%) patients were to have clinical hypothyroidism, and percentage of hypothyroidism was 42.3%. The incidence of hypothyroidism in our study was almost similar in range with other studies. The first occurrence of hypothyroidism was seen at 6 months after radiotherapy in our study. A study of Mercado *et al*. reported, with a median follow-up of 4.4 years, 48% and 67% of patients were developed subclinical hypothyroidism, and clinical hypothyroidism, respectively, with Kaplan–Meier survival curves projected 5 and 8 years for the development of subclinical hypothyroidism, and clinical hypothyroidism, respectively, when patients with head and neck malignancies were treated with external beam radiotherapy with or without concurrent chemotherapy.[14] The median time for the development of hypothyroidism was 1.4 years. In a study by Turner *et al*., 14.3% incidence of clinical and 23.8% subclinical hypothyroidism following radiotherapy to the whole of the thyroid gland.[15] The study estimated that up to 40% of the patients may become hypothyroid by 5 years. According to the study report of Aich *et al*., the overall incidence of clinical hypothyroidism patients was 17.8%, and subclinical hypothyroidism was 21.8%, and

hypothyroidism at the end of 2 years was detected as early as 6 weeks of follow-up period.[13] These findings suggest that post-radiotherapy hypothyroidism should be considered during the entire follow-up period, especially during the first 18 months.

In our study at 36 months of follow-up among male patients, 16 (20%) of 80 and among female patients, 6 (22.2%) of 27 developed hypothyroidism. Hancock *et al*. reported that relative risk of hypothyroidism more in female patients and Posner *et al*. reported that the incidence of hypothyroidism in female patients was more than 20%.[16,17] Post-radiotherapy hypothyroidism as it is a delayed effect, it is expected that with the passage of time the incidence will increase.

In our study, radiation dose was 60 Gy to 66 Gy. Hancock *et al*. reported that radiation dose-range of 3000–8000 rads is required to produce hypothyroidism.[16]

In our study at 36 months of follow-up, 10 (19.2%) patients in concurrent chemoradiation group developed hypothyroidism; incidence was more compared to only radiotherapy group 5 (9.6%) and 7 (13.4%) patients in neo-adjuvant chemotherapy followed by radiotherapy group. Aich *et al*. reported that the incidence of hypothyroidism with radiation alone was 16.6% and addition of chemotherapy with radiotherapy incidence was 21%.[13] Posner *et al*.,[17] Weissler and Berry,[18] and Sinard *et al*.[19] found no effect of combination chemotherapy on the thyroid gland in patients with head and neck malignancies.

However, this study contains a small number of patients and comparatively short period of follow-up that represents a major limitation for the conclusion.

CONCLUSION

Early diagnosis of clinical and subclinical hypothyroidism is a major problem in post-radiotherapy head-neck cancer patients. Hypothyroidism develops as early as 1 month after radiotherapy but may be delayed onset more than 5 years later. The incidence of hypothyroidism varies in between 3 and 40% and also incidence increases with time; usually, peak incidence has been seen at 2–3 years. It is recommended that serum TSH and free T4 have been estimated before initiation of radiotherapy and post radiotherapy at regular interval 6–12 months and carried out lifelong and physicians should not neglect to evaluate thyroid function of post-radiotherapy head and neck cancer patients. Early intervention with levothyroxine therapy should be initiated for all patients with clinical and subclinical hypothyroidism to prevent complications.

The newer technologies such as intensity-modulated radiotherapy and three-dimensional conformal radiotherapy can reduce the radiation dose to the thyroid gland and reduce the incidence of hypothyroidism.

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