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HYPOTHYROIDISM IN HEAD AND NECK CANCER PATIENTS AFTER RADIATION TREATMENT A TERTIARY CANCER CENTRE STUDY

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ABSTRACT

Background: Head and neck cancers is one of the most common malignancy in India. Radiation treatment is an integral part in the treatment of these patients. Hypothyroidism is a major radiation toxicity among these patients. But studies focusing on this are less in Indian population. **Objectives:** Primary objective of the study is to estimate the proportion of hypothyroidism in head and neck cancer patients after radiation treatment. **Materials and Methods:** This is an observational study of biopsy proved head and neck cancer patients who are selected either for definite or adjuvant radiation or chemoradiation. Baseline thyroid function test (TFT) prior to radiation treatment must be normal and the patients are monitored for TFT at three monthly intervals. Patients were treated with radiation treatment with radical radiation doses of 66Gy/33 fr, 66Gy/30fr or 60 Gy/30 fr based on the clinical scenario. Some patients received concurrent chemo radiation while others received neo adjuvant chemotherapy. **Results:** 61 patients were recruited for the study. Laryngeal cancers (39.3%) formed the most common subsite followed by oral cavity cancers (23%). Total incidence of hypothyroidism was 26.3%. Median time to development of hypothyroidism was 47 months (95% CI 28.87-65.121months).

KEYWORDS: chemoradiation, thyroid function test (TFT).

INTRODUCTION

Head and neck cancers form a major share of cancers in India. Lip and oral cavity cancers are the third most frequent cancers in Indian population They are the most frequent cancers among males while other pharyngeal cancers form the fifth most frequent cancers. It is one of the commonest malignancies encountered in radiotherapy practice in Kerala where this study is conducted. Radiotherapy forms an integral part of management of head and neck cancer. It is used as sole modality as well as in combination with chemotherapy and surgery .With improved survival long term effects of radiotherapy assume greater importance. The thyroid gland which is situated in front of the trachea and secretes two very important hormones T3 and T4 which are needed for normal growth and development. Development of hypothyroidism is an important concern in radiotherapy of head and neck cancer.

Thyroid dysfunction after radiation treatment was first reported in 1929. The most common clinical late-effect of the thyroid gland irradiation in patients exposed to therapeutic doses (30-70 Gy) to the cervical region is primary hypothyroidism.[1] Radiation fields for most head and neck cancers include the region of the thyroid gland. Damage is caused by vascular damage, parenchymal cell damage and autoimmune reactions. The most common effect is hypothyroidism. It is commonly sub-clinical. In the majority of cases, subclinical hypothyroidism progresses to clinical hypothyroidism.[2] Subclinical forms can produce adverse effects like cardiac dysfunction, neuropsychiatric symptoms, elevated LDL and total cholesterol .Subclinical hypothyroidism may be missed if routine thyroid function test (TFT) is not done during follow up. But in low resource settings routine testing of thyroid dysfunction is not done. On literature search it is seen that Hypothyroidism after radiotherapy alone or in combination with surgery and/or chemotherapy for patients with head-neck cancers is reported between 17% and 51%.[3-6] This study attempts to identify the incidence of hypothyroidism after radiation treatment.

Objectives of the study

Primary objective of the study is to estimate the proportion of hypothyroidism in head and neck cancer patients after radiation treatment

Secondary objectives

1. To evaluate whether any correlation exists with the total dose and dose per fraction of radiation.

2. To estimate median time to development of hypothyroidism.

Inclusion criteria

1. Age - 18 to 80 years
2. ECOG PS - 0 to 2
3. CBC, LFT, RFT- within normal limits
4. T3, T4, TSH- within normal limits
5. Biopsy proved non metastatic head and neck cancer selected for radical radiation treatment

Exclusion criteria

1. Thyroid cancers
2. Metastatic head and neck cancers
3. Prior thyroidectomy
4. History of prior radiation to thyroid
5. Patients treated with IMRT technique

MATERIALS AND METHODS

This is an observational study conducted in 61 patients with histologically proven head and neck cancer treated radically with external beam radiation. All patients satisfying the inclusion and exclusion criteria were included in this study. A baseline thyroid stimulating hormone (TSH) was done prior to start of radiotherapy. Patients who were treated using 2D/3D conformal planning using LINAC or Cobalt 60 teletherapy machine were included in the study. Radiation portals for each individual case was decided by the treating physician based on the radiation planning protocol of the institution. Radiation portals depend on the sub site, stage and the target volumes to be covered. Common fields used were either two lateral portals or two lateral portals and an additional low anterior neck portal matched to the lateral portals. Some cases, especially after tracheostomy, two AP –PA portals were used and shifted to lateral portals sparing the spinal cord after reaching spinal cord tolerance. Commonly used radical radiation doses to primary disease were 66Gy/33fr, 66Gy/30 fr or 60Gy/30fr. Doses were selected by the treating physician based on the indication i.e.: definitive or postoperative and based on the volumes treated. Concurrent chemotherapy was added according to indications and patient performance status as per physician choice. Concurrent chemotherapy schedule was Cisplatinum 40mg/m2 weekly once. Some patients received neo adjuvant chemotherapy based on the sub-site and stage of the disease.

Patients were followed up at 1 month following radiation and thereafter at 3-4 monthly intervals. Follow up included clinical examination, ENT evaluation and T3, T4 and TSH estimation. Imageology was done as per the need based on clinical findings. If there was elevation in TSH alone, they were considered to have subclinical hypothyroidism and if there was accompanying decrease of T3 and T4 they were considered to have clinical hypothyroidism. Any discordance in results was verified using free T3 (FT3) and free T4 (FT4) values.

Statistical Analysis

Data were coded and entered into Microsoft excel and analysed using SPSS version 16. Association between hypothyroidism and categorical variables were tested using fishers exact tests .For continuous variables Mann Whitney U tests were used. Median time to development of hypothyroidism was determined using Kaplan Meir analysis.

RESULTS

The analysis included 61 patients with head and neck cancer and satisfying the selection criteria. Patients in this study aged from 36 to 80 years with a median of 60 years .Ninety percent of them were males. Laryngeal cancers (39.3%) formed the most common subsite followed by oral cavity cancers (23%). T and N stages were available for 60 cases and the remaining one case was a case of recurrent paraganglioma. Most cases were T3 tumours and N1. Seven (11.5%) cases received postoperative radiation while majority received radiation as definitive local treatment. 50 patients (82 %) received chemotherapy prior to radiation. 21.3% received concurrent chemotherapy with cisplatin 40 mg/m2 weekly. Two patients received both neo-adjuvant and concurrent chemotherapy. Most common chemotherapy regimens used were 5 FU-cisplatin followed by Docetaxel/Cisplatinum/5FU (TPF). Other agents included methotrexate, carboplatin and paclitaxel. Table 1 shows the baseline characteristics of the group.

Table 1: Baseline characteristics.

Variable	Description	Number	Percentage
Gender	Male	55	90.2
	Female	6	9.8
Site	Oral cavity	14	23.0
	Nasopharynx	3	4.9
	Oropharynx	11	18.0
	Hypo-pharynx	7	11.5
	Larynx	24	39.3
	Salivary gland	1	1.6
	Others	1	1.6
T	1a	4	6.5
	1b	1	1.6

	2	17	27.8
	3	21	34.4
	4	1	1.6
	4a	13	21.3
	4b	3	4.9
N	0	8	13.1
	1	26	42.6
	2	1	1.6
	2a	2	3.3
	2b	12	19.7
	2c	8	13.1
	3	3	4.9
Surgery	No	54	88.5
	Yes	7	11.5
Concurrent chemo	No	48	78.7
	Yes	13	21.3
Neo adjuvant chemo	Yes	50	82
	No	11	18

Median follow up period was 9 months. During follow up 12 patients (19.7%) developed subclinical hypothyroidism and 4(6.6%) patients developed clinical hypothyroidism amounting to a total incidence of 26.3%. Four patients (6.6%) developed hyperthyroidism. Median time to development of hypothyroidism was 47 months (95% CI 28.87-65.121months).The probability of being non hypothyroid at 5yrs was 41.7%.

There was no association of hypothyroidism with gender, prior neck dissection, neo adjuvant or concurrent chemotherapy. Patients treated with a 3 field technique including a separate low anterior neck field did not show significant difference in incidence of hypothyroidism as compared to others.

Table 2 shows association between different variables and hypothyroidism.

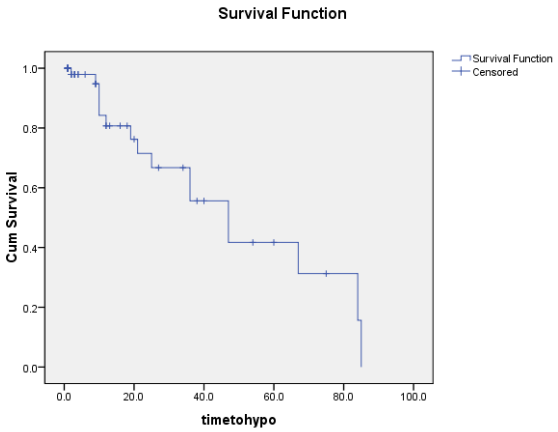

Table 2: Association between selected variables and hypothyroidism.

	Non hypothyroid	hypothyroid	p value
Concurrent chemo No	38	10	0.083
Yes	7	6	
Surgery Yes	5	2	1.000
No	40	14	
Neck dissection Yes	3	0	0.560
No	42	16	
low anterior field yes	30	13	0.350
No	15	3	
Neo adjuvant chemo			

Yes	38	12	0.457
No	7	4	
Gender male	42	13	0.179
Female	3	3	
Dose per fraction	2Gy	2.2Gy	0.030
Total dose	66Gy	60Gy	0.039
Time to hypothyroidism	3 months	23 months	<0.001

Dose per fraction and time since irradiation were related significantly to development of hypothyroidism. People who developed hypothyroidism had received a median dose of 2.2 Gy per fraction whereas others received a median dose of 2 Gy per fraction. Median time to development of hypothyroidism was 23 months in hypothyroid group. For patients who remained euthyroid at end of study, the median follow up period was only 3 months .The difference was significant with a p value of <0.001.

DISCUSSION

The pathophysiology of radiation induced thyroid dysfunction is not completely understood, but may involve vascular damage, fibrosis of the capsule which limits compensatory enlargement and formation of anti-thyroid antibodies. The chance of developing hypothyroidism becomes greater as the target tissue is closer to the thyroid gland and hence is high following head and neck irradiation especially glottic cancers where most of the thyroid tissue is irradiated. The results from this study show that 26.3% patients developed hypothyroidism.

This is consistent with other studies. On Literature review, a study by Boomsma et al rate of subclinical hypothyroidism range from 23 to 53% .Study by kumar etal found rates of subclinical hypothyroidism at 24% and symptomatic hypothyroidism at 6%.Study by Srikantia et al found an incidence of 42.2 % of hypothyroidism of which about 11.1% was subclinical.

Thyroid function tests may be costly in a low resource setting but this study shows that the about one fourth of patients treated develop hypothyroidism and hence TFT should be done as part of follow up. Patients may present with nonspecific constitutional symptoms and neuropsychiatric complaints which may be easily overlooked in the absence of screening. Many of these symptoms may be attributed to malignancy or chemotherapy if the patient is taking any.

In this study it is seen that development of hypothyroidism has no correlation with sex or age of patients.[7] Addition of chemotherapy either as concurrent or neo-adjuvant did not have any relation to the development hypothyroidism in our cohort of patients which is consistent with other studies in the literature.[8]

Screening with TSH might be enough in low resource settings since we are looking here for primary hypothyroidism. Increased LDL cholesterol and cardiac mortality are linked with prolonged elevation of TSH levels. Thyroid function probably worsens with time as indicated by the significantly different median follow up periods for euthyroid and hypothyroid patients and hence should be considered even during late follow up.

Limitations of this study include an inability to relate thyroid dysfunction with the actual dose received by the thyroid gland and use of thyroid testing performed at multiple laboratories. So common cut off values or standardization could not be done. This study has also not incorporated patients treated with newer conformal technique like IMRT.

CONCLUSION

Head and Neck cancer patients after radiation treatment and during follow up may complain of tiredness and other systemic symptoms. Majority of the physicians ignore the fact that there is high chance of hypothyroidism in these patients and they simply attribute everything to disease or treatment sequelae. As hypothyroidism is a potential reason for this and as it is a treatable pathology, it must be detected early. From this study we arrive at a conclusion that there must be a protocol for detection of hypothyroidism in post radiation head and neck cancer patients.

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