Relation of External Beam Radiotherapy Dose with Subclinical Hypothyroidism in Patients undergoing Adjuvant Neck Radiation after Surgery for Squamous Cell Carcinoma of Head and Neck

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ABSTRACT

The objective of this study was to find out the radiation dose relationship with subclinical hypothyroidism in the postoperative head and neck squamous cell carcinoma patients, who underwent adjuvant neck external beam radiotherapy. It was a prospective cohort study done between June 2018 and January 2020. One hundred patients, who were fulfilling the criteria of histological proven postoperative head and neck squamous cell carcinoma (SCC) of AJCC 2018 stage I to III, were enrolled. Patients were irradiated for 50 Gy to the bilateral lower neck on a linear accelerator. A CT scan face and neck with contrast along with T3, T4, and TSH was done before and after 4 weeks of chemoradiotherapy. All the patients were kept on surveillance for every three months for one year with the above-mentioned CT scan and thyroid function test. Ten patients (10%) had received radiation dose less than 30 Gy to the thyroid gland, while 90 patients (90%) had received radiation dose >30 Gy to thyroid gland. After one year of completion of treatment, 27.8% patients (n = 25) developed subclinical hypothyroidism among those patients (n = 90), who received radiation dose more than 30 Gy to thyroid gland. None of the patients had subclinical hypothyroidism among those patients (n =10), who received radiation dose below 30 Gy to thyroid gland (p= 0.062).

Key Words: *Head and neck cancer, Neck radiotherapy, Subclinical hypothyroidism.*

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Subclinical hypothyroidism is a late effect of neck external beam radiotherapy. It is defined as mild or no symptoms of hypothyroidism and mildly low T3, T4 and slightly raised TSH. The common causes of subclinical hypothyroidism are Hashimoto thyroiditis, previous thyroid surgery, drugs or previous radiotherapy.[1] Latest quantitative analyses of normal tissue effects in the clinic (QUANTEC) parameters does not clearly show the actual tolerance doses of the thyroid gland, dose volume histograms (DVH's) of thyroid gland, and incidence of radiation-induced hypothyroidism in the patients undergoing neck radiotherapy.[2] Radiation induced subclinical hypothyroidism in the survivors of head and neck cancer may mislead to other late effects; thus has to be evaluated on regular basis, which is usually not seen in the clinical practice in which subclinical hypothyroidism is the diagnosis of exclusion.

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Mostly, due to the absence of symptoms, it is not noticed and treated. However, if detected early, thyroxin replacement therapy can be administered to prevent the eventual symptomatic hypothyroidism. Hypothyroidism is considered a late appearing complication of head and neck radiotherapy; and the time to onset can be several years following therapy resulting in the need for chronic hormone replacement. There was no QUANTEC report focusing on thyroid complications, but Vogelius *et al*. published a systematic review on risk factors for radiation-induced hypothyroidism, identifying the following significant risk factors: female gender; surgery involving the neck or thyroid gland; and Caucasian race. Furthermore, they estimated the mean thyroid dose of 45 Gy was resulted in 50% complication rate.[3] A study showed relationship of radiation dose and volume of irradiated thyroid gland and delivered up to 40 Gy dose to thyroid gland with significant appearance of hypothyroidism.[4]

The objective of this study was to find out the relation of subclinical hypothyroidism with the external beam radiation dose, and to set a cut-off level of radiation dose above which significant hypothyroidism could be predicted.

This study was approved by the Hospital Ethical Committee; and patient consent was obtained before start of the study. This study was conducted at Atomic Energy Medical Centre (AEMC), JPMC, Karachi. In this study, those patients have been included, who had

undergone surgery for squamous cell carcinoma of head and neck with no distant metastasis, either pT1-2 N0 having close margins or pathological node positive with pT1-T4 disease, according to the AJCC staging 2018. All the patients had no residual disease before chemoradiotherapy on CT scans and had euthyroid status. Patients who had any prior disease of thyroid, inoperable head and neck SCC, gross residual disease after surgery, or recurrent tumors were, excluded.

All patients were treated by bilateral face and neck external beam radiotherapy and primary sites included were: mobile tongue, hard palate, lips, buccal muocsa, floor of mouth, and retromolar trigone reaching to the midline. All the patients were delivered external beam radiotherapy with concurrent intravenous cisplatin chemotherapy. As per literature review, impact of cisplatin, as confounding variable on subclinical hypothyroidism, was negligible. The treatment regime included 100 external beam radiotherapy of the neck for 66 Gy to face and upper neck; and 50 Gy dose @ 2 Gy/ fraction with offcord on 44 Gy on linear accelerator by the 3DCRT using Siemens 24 slice dedicated CT simulator. Dosimetrist work station was used as contouring tool and Prowess Panther as planning software. All the contourings and plans were reviewed and approved subsequently by two radiation oncologists and physicists, respectively. SPSS version 21 was used for data analysis. Categorical data were given as number and percentage while quantitative data as mean ± S.D. Fisher's exact test was applied to determine association among categorical variables. The p value of 0.05 was accepted as significant.

Ten patients had radiation dose less than 30 Gy to thyroid gland, while rest of the 90 patients received dose more than 30 Gy to thyroid gland. Patients were investigated *via* CT scan and T3, T4 and TSH after 4 weeks of completion of chemoradiation; and all these investigations were normal. All the patients were followed up *via* 3-monthly intervals with same investigations upto one year. Male patients were 85%, while female patients were 15%. Mean age was 39.9 ± 8.9 years and age range was 26-61 years.

After one year, among the 90 patients who received radiation dose of >30 Gy to thyroid gland, 25 (27.8%) patients [23 (92% men and 2 (8%) women] developed subclinical hypothyroidism; there were none among the 10 patients, who had received <30 Gy radiation dose.

Subclinical hypothyroid patients had either symptoms like weakness, irritability, cold intolerance (25%) or having no symptoms at all (75%). All the 27.8 % patients, who developed subclinical hypothyroid, had mild low T3, T4 and mild raised TSH levels. All the patients had normal CT scan on follow-up visits.

Subclinical hypothyroidism is an important late effect induced by radiotherapy after the curative treatment. Some of the studies reported 19 % to 51% of the patients developing radiation-induced hypothyroidism. Survivors of postoperative head and neck cancer encounter various treatment-associated complications; and hypothyroidism worsens the situation. Hypothyroidism could be explained by radiotherapy-induced direct cell injury, microvascular insult and immune- mediated damage, which resulted in reduction of the thyroglobulin production by the thyroid gland resulting in reduced synthesis of thyroxine and tri-iodothyronine.[5] No definite dose constraint for thyroid radiation-induced toxicity is available as shown earlier in QUANTEC. Few larger series have shown some specified dose volume histogram (DVH). Some studies showed V30 of 60% of thyroid gland, without hypothyroidism, and 78% in those with hypothyroidism: identifying V30 <7cm^3 as the optimal cutoff in a cohort of Hodgkin's lymphoma patients and showing an association between mean thyroid dose <30 Gy and a lower risk of hypothyroidism. Similarly, thyroid V45 was identified as important by other studies, either recommending keeping V45 <50% as a cut-off; sparing at least 5 cm^3 of the thyroid or keeping the mean thyroid dose <45 Gy, as this was associated with significantly lower risk of hypothyroidism. One study with very long follow-up identified a thyroid V50 ≤60% as an important cut-off, which is less conservative compared to most of the other identified dose-volume constraints.

It was concluded that 30 Gy is the not significant cut-off level of the radiation dose; and above this dose, subclinical hypothyroidism chances increased. However, larger prospective randomised trials, using different techniques like IMRT, SBRT are needed to find the precise DVH estimation correlated with clinical findings. Therefore, it will help recommend prophylactic treatment for hypothyroidism based on DVH.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
NU: Design, literature review, data collection, drafting, write-up, statistical analysis and final review.
MI: Data collection and final write-up.
HH: Drafting and write-up.

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