ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 16, Issue 11, 2023

Online - 2455-3891
Print - 0974-2441

Research Article

HYPOTHYROIDISM IN HEAD-AND-NECK CARCINOMA PATIENTS AFTER RADIATION

SUBHASH, GAURAV GUPTA, RAJKUMAR VERMA, MUKUL YADAV*

Department of ENT, Sardar Patel Medical College, Bikaner, Rajasthan, India.
***Corresponding author: Mukul Yadav; Email: subhashsihag20@gmail.com**

Received: 09 May 2023, Revised and Accepted: 23 June 2023

ABSTRACT

Objective: The objective of the study was to determine the incidence of clinical hypothyroidism in patients undergoing radiation therapy for head-and-neck carcinomas.

Methods: One hundred and fifty patients with head-and-neck cancers visiting the Department of Otorhinolaryngology and head-and-neck surgery and undergoing treatment after histological confirmation at the Department of ENT and Radiation Oncology at Sardar Patel Medical College, Bikaner, Rajasthan, from January 2022 to January 2023 were taken up for the study. Tumor response and symptom relief were monitored at the completion of treatment, at 3 months, and at 6 months.

Results: Mean age of 51.42±12.24 years (21–78 years), 59.33% were males, and 63.34% of the study population was residing in rural areas. About 30.67% were in the oral cavity followed by 28.67% and 28.5 in the larynx and nasopharynx, respectively. Mean FT4 was 1.35±0.40 before radiotherapy and decreased to 1.20±0.43 after 3 months and 1.12±0.40 after 6 months of radiotherapy ($p<0.0001$*). Mean thyroid stimulating hormone was 2.14±2.50 before radiotherapy and increased to 3.55±4.5 after 3 months and 4.1±6.8 after 6 months of radiotherapy ($p<0.0001$*). At 3-month follow-up, 8% had clinical hypothyroid, at 6-month follow-up, 18% had clinical thyroid ($p<0.05$).

Conclusion: Thyroid hormone monitoring following radiotherapy for head-and-neck cancers should incorporate part of follow-up of these patients, especially those patients who receive chemotherapy with radiotherapy.

Keywords: Hypothyroidism, Head-and-neck carcinoma, Radiation.

 DOI: http://dx.doi.org/10.22159/ajpcr.2023v16i11.48650. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Head-and-neck malignancies are the seventeenth-most common malignancies, worldwide and the second-most common malignancy in India (1st-most common in males while 4th-most common in females), with approximately 19.2 million new cases and 9.95 million cancer-related deaths in 2020 and 50.5 million prevalent cases in all age groups [1]. India is a single country contributing to 10.43% of the global cancer burden and 7.05% of deaths in 2020 GLOBOCAN [2].

Radiotherapy is one of the main treatment modalities for head-and-neck cancer and the patient's neck is often included in the radiation field when receiving radiotherapy resulting in damage to the normal tissue of the neck, especially the thyroid gland resulting in radiation-induced hypothyroidism [3]. With the advent of intensity-modulated radiotherapy (IMRT) which facilitated more conformity in dose shaping, providing higher doses to target volumes, has limited the dose to the organ at risk, thus leading to less toxicity [4,5].

The incidence of post-radiotherapy hypothyroidism as reported in various literature varies from as low as 6% to as high as 68% [6,7]. Hypothyroidism also results in long-term complications with respect to cardiac and general morbidity. Such morbidity in cancer survivors can be of immense physical, emotional, social, and economic problems. Thus, early detection and treatment of post-radiotherapy hypothyroidism can result in the avoidance of such complications and help in improving the quality of life. Most of the guidelines have been developed on the basis of the western data. The applicability of the same to the Indian population is not well defined, especially in view of the heterogeneity of data, originating from different populations of the world. This not only includes the incidence but also the time of occurrence of hypothyroidism post-radiotherapy.

This study is an endeavor to determine the incidence-associated factors in the development of hypothyroidism including the temporal association of the incidence with respect to the population from the Indian subcontinent.

Aim

The aim of the study was to determine the incidence of clinical hypothyroidism in patients undergoing radiation therapy for head-and-neck carcinomas.

METHODS

One hundred and fifty patients with head-and-neck cancers visiting the department of otorhinolaryngology and head-and-neck surgery and undergoing treatment after histological confirmation at the Department of ENT and Radiation Oncology at Sardar Patel Medical College, Bikaner, Rajasthan, from January 2022 to January 2023 were taken up for the study.

Adult patients with non-metastatic head-and-neck carcinoma, without any intracranial extension, of the nasopharynx, sinonasal cavity, oropharynx, oral cavity, hypopharynx, larynx, carcinoma of unknown primary, receiving radiotherapy (>45 Gy) as part of treatment, radiation field extending to lower neck, unilateral or bilateral, and performance score were included in the study. Known to have hypothyroidism, at the time of screening, history of hypothyroidism in the past, currently on supplements, history of previous exposure to radiation therapy in head-and-neck region, and patient not willing were excluded from the study.

The patients who fulfill the above-mentioned criteria were explained the aims, objectives, protocol, and investigations, required for the study both verbally and by a written informed consent document, as approved by the institutional review board and ethics committee

(hereafter referred to as IRB) in a language patient can understand. After the informed consent was obtained, they were screened for any thyroid abnormalities. Once, they were found to be fitting into the euthyroid group by the blood tests. They were included as the part of the study. Patients, who were found to be hypothyroid on investigations, were not included in the study. The patients were started on treatment as required as per their treatment plan and modality of radiation chosen by the patients (conventional 2D cobalt, 3 DCRT, and IMRT) with or without chemotherapy, with or without biological agents.

The patients were followed at the following schedule.

a. At 18 weeks (3 m) from the date of completion of radiotherapy
b. At 30 weeks (6 m) from the date of completion of radiotherapy.

Hypothyroidism as defined biochemically or subclinically as raised thyroid stimulating hormone (TSH) only (normal 0.3–4.5), or clinical hypothyroidism with raised TSH and a low T4 (normal 4.5–12.5), free T4 (0.8–2). Tumor response and symptom relief were monitored at the completion of treatment, at 3 months, and at 6 months.

Required approval was taken from the ethics committee and research committee. Written informed consent was taken from all the patients who were enrolled in the study.

RESULTS

Maximum 26% cases were in 51–60 years age group whereas a minimum 10% were in 71–80 years group with a mean age of 51.42±12.24 years (21–78 years). About 59.33% were males, and 63.34% of the study population were residing in rural areas (Table 1).

In our study, a cancer site maximum 30.67% were in the oral cavity followed by 28.67% and 28.5 in the larynx and nasopharynx, respectively, whereas a minimum 4.675 were in the sino nasal followed by 8% oropharynx (Fig. 1).

According to TNM staging maximum 64% were in T4 followed by 25.33% in T3, whereas a minimum 4% were in T1 followed by 8.67% in T2. About 43.33% were in N1 followed by 36.67% in N2, whereas a minimum 10% were in N0 and N3. Maximum 4% were in M1 whereas a minimum 96% were in M0. According to histopathology maximum 70% were in moderately differentiated followed by 20% were well-differentiated whereas a minimum 10% were poorly differentiated (Fig. 2).

According to chemotherapy maximum of 74.67% had taken chemotherapy whereas a minimum 25.33% did not undergo chemotherapy. Maximum 89.29% had taken three cycles whereas minimum 5.36% each had one and two cycles, respectively. The mean duration of radiotherapy was 49.58±10.5 days. Maximum 74.66% needed both chemotherapy and radiotherapy whereas minimum 25.34% cases were treated by radiotherapy alone and 5.44% cases were treated by modified radical neck dissection whereas 4.66% were treated by wide local excision (Table 2).

Mean FT4 was 1.35±0.40 before radiotherapy and decreased to 1.20±0.43 after 3 months and 1.12±0.40 after 6 months of radiotherapy (p<0.0001*). Mean TSH was 2.14±2.50 before radiotherapy and increased to 3.55±4.5 after 3 months and 4.1±6.8 after 6 months of radiotherapy (p<0.0001*).

According to the thyroid function test 100% were normal at baseline. At 3-month follow-up, maximum 92% had a normal function, followed by 8% clinical hypothyroid. At 6-month follow-up, a maximum 82% had a normal function and 18% had clinical thyroid. The difference was statistically significant (0.0001*) (Table 3).

Hypothyroidism was found in 44.73% of cases <40 year group and in 25.97% cases in 41–60 year age group. No cases were found in > 60-year age group (p<0.069). Hypothyroidism was found equally in both surgery modalities. Hypothyroidism was found in 29.46% of cases with chemotherapy and radiotherapy whereas 10.52% in only radiotherapy (p<0.05). Hypothyroidism was found in 31.57% of cases of radiotherapy by 200 cGy × 33 fractions whereas 2.77% cases of hypothyroidism were reported in the simultaneous boost technique (p=0.001*) (Table 4).

DISCUSSION

In our study, according to chemotherapy, maximum 74.67% had taken chemotherapy with 89.29% having taken three cycles and the mean duration of radiotherapy was 49.58±10.5 days, similarly reported by Kumari *et al*. [8].

Table 1: Sociodemography of study participants

Age (year)	Frequency	Percentage
21–30	20	13.33
31–40	18	12.00
41–50	38	25.33
51–60	39	26.00
61–70	20	13.33
71–80	15	10.00
Gender		
Male	89	59.33
Female	61	40.67
Residence		
Urban	55	36.66
Rural	95	63.34

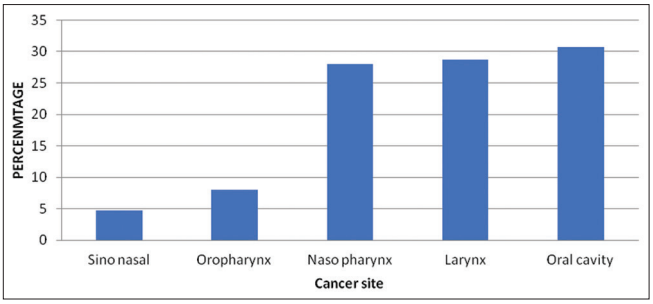

Fig. 1: Primary cancer site as seen among study participants

Table 2: Pattern of treatment received by study participants

Type of treatment	Frequency	Percentage
Chemotherapy and radiotherapy both	112	74.66
Radiotherapy alone	38	25.34
Surgery		
Wide local excision	7	4.66
MRND	8	5.44
No	135	90

MRND: Modified radical neck dissection

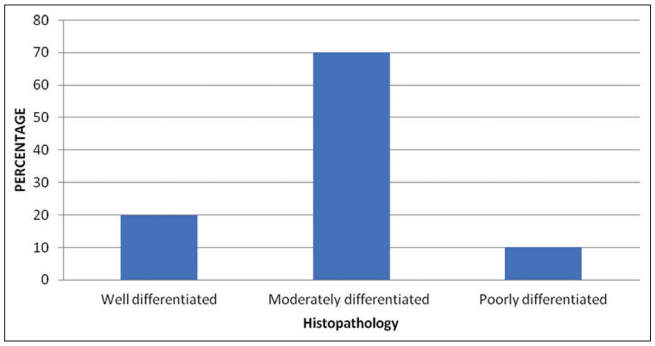

Fig. 2: Distribution of study participants as per histopathology

Table 3: Thyroid function test report of study participants

Thyroid function test	Before radiotherapy	After radiotherapy (at 3 months)	After radiotherapy (at 6 months)	p-value
FT4	1.35±0.40	1.20±0.43	1.12±0.40	0.0001*
TSH	2.14±2.50	3.55±4.5	4.1±6.8	0.002*
Normal thyroid function	150 (100%)	138 (92.00%)	123 (82.00%)	0.0001*
Clinical hypothyroidism	0 (0.0)	12 (8.00%)	37 (18.00%)	

TSH: Thyroid stimulating hormone. *significant

Table 4: Association of hypothyroidism with various parameters

Age (year)	Normal (%)	Hypothyroidism (%)	Total	p-value
<40	21 (55.26)	17 (44.73)	38 (100)	0.07
41–60	57 (74.02)	20 (25.97)	77 (100)	
>60	35 (100)	0	35 (100)	
Surgery				
Wide local excision	5 (71.43)	2 (28.57)	7 (100)	0.668
MRND	6 (75%)	2 (25)	8 (100)	
Chemotherapy				
Yes	79 (70.54)	33 (29.46)	112 (100)	0.034*
No	34 (89.47)	4 (10.52)	38 (100)	
Schedule (total dose)				
200 cGy×33 fractions (6600)	78 (68.42)	36 (31.57)	114 (100)	0.001*
Simultaneous boost techniques (Equivalent>66 Gy)	35 (97.22)	1 (2.77)	36 (100)	

MRND: Modified radical neck dissection

In our study, mean FT4 was 1.35±0.40 before radiotherapy and decreased to 1.20±0.43 after 3 months and 1.12±0.40 after 6 months of radiotherapy (p<0.0001*). Mean TSH was 2.14±2.50 before radiotherapy and increased to 3.55±4.5 after 3 months and 4.1±6.8 after 6 months of radiotherapy (p<0.0001*). Similarly, Bernát and Hrušák [9] found significant differences between TSH and FT4 levels, and a correlation between hormone levels and follow-up was also detected. Our study was in agreement with the study of Laway *et al.* [10] and Yoden *et al*. [11].

In our study, at 3 months 8% had clinical hypothyroid and at 6 months 18% had clinical hypothyroid (0.0001*), similarly reported in a study by Kumari *et al*. [8] and Fujiwara *et al*. [12].

In our study, hypothyroidism was found in 44.73% cases <40 year group and in 25.97% cases in 41–60-year age group. No cases were found in >60-year age group (p<0.069). These findings are similar of Koc and Capoglu [13]. Age was found not to influence the development of thyroid dysfunction in our study as dysfunction was distributed across the various age groups.

In our study, hypothyroidism was found in 29.46% of cases with chemotherapy and radiotherapy whereas 10.52% in only radiotherapy, and the difference between them was found to be statistically significant (p<0.05). On contrary, other studies by Immanuel *et al*. [14] and Langerman *et al*. [15] found chemotherapy not to have any effect on the development of thyroid dysfunction.

In our study, 75% of the patients were treated with both chemotherapy and radiotherapy with only 25% receiving radiotherapy alone. Concurrent use of chemotherapy with radiotherapy is expected to increase radio sensitivity of the thyroid gland and increase the incidences of thyroid dysfunction as witnessed in our study.

In our study, hypothyroidism was found equally in both surgery modalities (p>0.05) also similarly reported by Sinard *et al*. [16] in their study.

In our study, hypothyroidism was found in 31.57% cases of radiotherapy by 200 cGy × 33 fractions whereas 2.77% of cases of hypothyroidism was reported in the simultaneous boost technique (p=0.001*). On the contrary, Alterio *et al*. [17] have also reported that point dose does not correlate with the incidence of hypothyroidism.

This is probably because the thyroid gland itself may vary in position and depth from patient to patient and therefore the surface dose based on surface marking of the thyroid may not be representative of the dose received by the thyroid gland.

CONCLUSION

Thyroid hormone monitoring following radiotherapy for head-and-neck cancers should incorporate part of follow-up of these patients, especially those patients who receive chemotherapy with radiotherapy. Further studies can be done with a larger cohort and be followed up for a longer time to establish the incidences of development of thyroid dysfunction.

ACKNOWLEDGMENT

We owe an obligation of appreciation to the SP Medical College for help throughout the research exploration.

AUTHORS' CONTRIBUTION

All the authors have contributed equally.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR'S FUNDING

The writers thusly express that they got no monetary help for their examination, composing, or distribution of this paper.

REFERENCES

1. World. Globocan 2020: New Global Cancer Data. Geneva: Union Internationale Contra le Cancer; 2020. Available from: https://www.uicc.org/news/globocan-2020-new-global-cancer-data [Last accessed on 2023 Feb].
2. GLOBOCAN I. Iarc; 2020. Available from: https://www.356-india-fact-sheets.pdf.fr
3. Bhide SA, Nutting CM. Advances in radiotherapy for head and neck cancer. Oral Oncol 2010;46:439-41. doi: 10.1016/j.oraloncology.2010.03.005, PMID 20409746
4. Blanchard P, Bourhis J, Lacas B, Posner MR, Vermorken JB, Cruz Hernandez JJ, *et al.* Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: An individual

patient data meta-analysis of the meta-analysis of chemotherapy in head and neck cancer group. J Clin Oncol 2013;31:2854-60. doi: 10.1200/JCO.2012.47.7802, PMID 23835714

5. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, *et al*. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988;48:3282-7. PMID 3365707
6. IMRT Documentation Working Group, Holmes T, Das R, Low D, Yin FF, Balter J, *et al*. American society of radiation oncology recommendations for documenting intensity-modulated radiation therapy treatments. Int J Radiat Oncol Biol Phys 2009;74:1311-8. doi: 10.1016/j.ijrobp.2009.04.037, PMID 19616738
7. Choudhury A, Budgell G, MacKay R, Falk S, Faivre-Finn C, Dubec M, *et al*. The future of image-guided radiotherapy. Clin Oncol (R Coll Radiol) 2017;29:662-6. doi: 10.1016/j.clon.2017.04.036, PMID 28511968
8. Kumari S, Gondi J, Nemade H, Chandra Sekhara Rao LM, Gudipudi D, Rao TS. Hypothyroidism in carcinoma of the tongue with adjuvant treatment. Rambam Maimonides Med J 2017;8. doi: 10.5041/RMMJ.10290, PMID 28448252
9. Bernát L, Hrušák D. Hypothyroidism after radiotherapy of head and neck cancer. J Craniomaxillofac Surg 2014;42:356-61. doi: 10.1016/j.jcms.2013.09.009, PMID 24210455
10. Laway BA, Shafi KM, Majid S, Lone MM, Afroz F, Khan S, *et al*. Incidence of primary hypothyroidism in patients exposed to therapeutic external beam radiation, where radiation portals include a part or whole of the thyroid gland. Indian J Endocrinol Metab 2012;16:S329-31. doi: 10.4103/2230-8210.104078, PMID 23565416
11. Yoden E, Soejima T, Maruta T, Demizu Y, Nishimura H, Ejima Y, *et al*. Hypothyroidism after radiotherapy to the neck. Int J Radiat Oncol Biol Phys 2001;51:337-8.
12. Fujiwara M, Kamikonya N, Odawara S, Suzuki H, Niwa Y, Takada Y, *et al*. The threshold of hypothyroidism after radiation therapy for head and neck cancer: A retrospective analysis of 116 cases. J Radiat Res 2015;56:577-82. doi: 10.1093/jrr/rrv006, PMID 25818629
13. Koc M, Capoglu I. Thyroid dysfunction in patients treated with radiotherapy for neck. Am J Clin Oncol 2009;32:150-3. doi: 10.1097/COC.0b013e3181845517, PMID 19307948
14. Immanuel V, Sachdeva J, Singh N, Kingsley PA, Chandran RS. Evaluation of thyroid dysfunction in patients with head and neck cancer receiving radiation therapy or chemoradiation. Parameters 2019;10:V50.
15. Langerman A, Athavale SM, Rangarajan SV, Sinard RJ, Netterville JL. Natural history of cervical paragangliomas: Outcomes of observation of 43 patients. Arch Otolaryngol Head Neck Surg 2012;138:341-5. doi: 10.1001/archoto.2012.37, PMID 22431860
16. Sinard RJ, Tobin EJ, Mazzaferri EL, Hodgson SE, Young DC, Kunz AL, *et al*. Hypothyroidism after treatment for nonthyroid head and neck cancer. Arch Otolaryngol Head Neck Surg 2000;126:652-7. doi: 10.1001/archotol.126.5.652, PMID 10807335
17. Alterio D, Jereczek-Fossa BA, Franchi B, D'Onofrio A, Piazzi V, Rondi E, *et al*. Thyroid disorders in patients treated with radiotherapy for head-and-neck cancer: A retrospective analysis of seventy-three patients. Int J Radiat Oncol Biol Phys 2007;67:144-50. doi: 10.1016/j.ijrobp.2006.08.051, PMID 17084554