Thyroid function status evaluation in patient post-radiotherapy for nasopharyngeal carcinoma: A retrospective study

Loh Zheng Hao, MBBS[1], Sakinah Mohamad, MMed (ORL-HNS)[1], Gan Boon Chye, MMed (ORL-HNS)[2], Zahirrudin Zakaria, MS (ORL-HNS)[2], Irfan Mohamad, MMed (ORL-HNS)[1]

[1]Department of Otorhinolaryngology-Head & Neck Surgery, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [2]Department of Otorhinolaryngology-Head & Neck Surgery, Penang General Hospital, Penang, Malaysia

ABSTRACT

Introduction: Nasopharyngeal carcinoma (NPC) is among the most common malignancy in Malaysia. Radiation-induced hypothyroidism has been reported in other countries. However, in Malaysia, no studies were ever done to determine the effect of radiation on hypothyroidism. The objective of this study is to evaluate the practice of taking thyroid function test (TFT) and determine hypothyroidism post-radiation in patients with NPC.

Materials and Methods: A retrospective study on the symptoms and results of TFT according to the dosage of intensity-modulated radiotherapy (IMRT) given to patients with NPC. Data were traced and analysed.

Results: A total of 78 patients were identified. All patients received IMRT with 33–35 fractions of radiotherapy (RT) with total dosage of 66–70 Gray given. Not all patients had their thyroid function status measured routinely. Twelve patients did have symptoms of hypothyroidism. TFT were obtained in this group but the results were normal. No correlation was found between RT and hypothyroidism.

Conclusion: There was no correlation between IMRT and the development of hypothyroidism. A prospective study with better control of inclusion and exclusion criteria, and longer follow-up period with TFT, is needed to demonstrate the consistency of these findings.

KEYWORDS:
Hypothyroidism; nasopharyngeal carcinoma; radiation-induced

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is the fourth most common malignancy in Malaysia.[1] It is common among the Chinese, followed by natives of Borneo (especially Bidayuh) and Malay.[1] Depending on the year after completion of treatment, follow-up varies from every month to every year.[1] The mainstay treatment of NPC is radiotherapy (RT), or in combination with chemotherapy. Recent management of NPC usually involved the addition of chemotherapy to RT. A meta-analysis conducted in 2015 confirmed that the addition of chemotherapy to RT significantly improves survival in patients with loco-regionally advanced NPC.[2]

Conventional RT involved the delivery of a complete radiation dose over several occasions. It uses high-energy X-rays to shrink or destroy tumour cells. The gap in between radiation allowed for normal cells to heal. Intensity-modulated radiotherapy (IMRT) uses a linear accelerator to precisely deliver a higher radiation dose conform to the shape of the tumour. By doing so, it reduces the damage to surrounding tissues. Study published in 2016 showed IMRT usage is gaining popularity with only 1.5% usage in 2000 but increased to 48.6% in 2007 while the usage of conventional RT decreased from 98.5% to 51.4 %.[3] No study after 2016 was found on literature search. There were no studies in Malaysia showing the percentage of IMRT and conventional RT in use currently.

Radiation-induced hypothyroidism is not uncommon.[4,5] The incidence of hypothyroidism in NPC patients is increasing trend based on duration post-RT.[4,5] The level of thyroid hormone is in a decreasing trend post-RT for 0 to 30 months and reaches a steady state by 36 months.[2] Damage to the hypothalamus-pituitary-thyroid axis may result in hypothyroidism.[6] Thyroxine is usually started as treatment if hypothyroidism is detected.[6] The incidence of radiation-induced hypothyroidism of head and neck cancer is 6–20% while the incidence of subclinical hypothyroidism is 24–50%.[7] Up to 23.2% of patients developed radiation-induced hypothyroidism in NPC.[5] Evaluation of thyroid function is recommended at 1,2 and 5 years.[8]

IMRT showed a reduction in radiation xerostomia in early-stage disease.[8] It poses possibility that it will also reduce the hypothyroidism complication. Radiation-induced hypothyroidism is significantly related to the patient's age, radiation dose, gender and clinical stage.[9] The usage of neoadjuvant RT with IMRT and concurrent chemoradiotherapy with adjuvant chemotherapy showed that both results were similar.[10]

This study aims to determine the level of thyroid function post-RT in NPC patients. Our specific objectives were first to identify the number of patients' thyroid function test (TFT) taken among study subjects and the time it was taken. Secondly to determine the association between underlying illness, gender, stage at diagnosis, type and dose of RT and the proportion of causation of radiation-induced hypothyroidism.

This article was accepted: 26 February 2023
Corresponding Author: Irfan Mohamad
Email: irfankb@usm.my

Table I: Percentage of patients according to fraction of RT

	Frequency	Percentage
Tx32	3	3.8
Tx33	28	35.9
Tx35	47	60.3
Total	78	100.0

Table II: Number of patients with symptoms and percentage of TFT taken

Variables		n	(%)
Symptomatic hypothyroidism	No	66	84.6
	Yes	12	15.4
Sample TFT taken	No	66	84.6
	Yes	12	15.4

Table III: Correlation between comorbidities, fraction of RT and hypothyroidism

Variables		Crude Odd Ratio (OR)	95% (Lower,	CI Upper)	*p* value*
Age		1.020	.974	1.069	.396
DM	No	1			
	Yes	1.409	.144	13.820	.768
HPT	No	1			
	Yes	.625	.124	3.156	.569
HLP	No	1			
	Yes	.509	.059	4.392	.539
IHD	No	1			
	Yes	1.409	.144	13.820	.768
Comorbidities	No	1			
	Yes	.900	.174	4.649	.900
Tumor	1	1			
	2	.279	.028	2.751	.274
	3	.679	.109	4.240	.678
	4	1.484	.340	6.478	.599
Nodular	0&1	1			
	2&3	3.000	.737	12.219	.125
Metastasis	0	1			
	1&x	.284	.034	2.374	.245
Treatment	Tx32+33	1			
	Tx35	.910	.261	3.174	.882

MATERIALS AND METHODS

Study Design

This was a retrospective study approved by Human Research Ethics Committee USM (JEPeM Code: USM/JEPeM/21030244) on 22nd August 2021. National Medical Research Register (Research ID: 58392) was obtained on 30th April 2021.

The sample was obtained from a list of patients under the follow-up of Otorhinolaryngology clinic in Penang General Hospital (PGH), as defined in the inclusion and exclusion criteria. The inclusion criteria included all NPC patients who had completed RT. This study excluded patients with recurrence and those who had previous thyroid surgery. A convenient sampling method was used for the selection. Planning of oncological treatment was done by the radiation oncologist as per standard practice.

Subjects

All patients diagnosed with NPC from the year 2016 to 2020 who came for follow-up in PGH. Data obtained from cancer registry and records of patients were traced. A total of 113 patients were diagnosed with NPC and came for follow-up in PGH. From an expected prevalence of 20%, the calculated sample size was 78, from a finite population of 113.[6]

Sample Collection

All data were collected using the study proforma which included the patient's age, gender, race, comorbidities, number of fractions of RT received, whether a TFT was taken, and the results if the TFT taken.

Statistical Analysis

Categorical data were presented as frequency and percentage while numerical data were presented as mean and standard deviation (SD). We applied simple logistic regression tests in the univariate analysis. Variables comparison with a P-value less than 0.05 is considered as significant. The data were analysed using SPSS software version 26.

RESULTS

The data showed that up to 86% of cases were from Chinese (Figure 1). The majority of cases came from the age group 41–60 (Figure 2).

From the 78 samples collected, the mean age of patients at diagnosis was 53.68 years old. About 60.3% of patients (n=47) received 35 fractions of RT, meanwhile 35.9% of patients (n=28) received 34 fractions of RT and 3.8% of

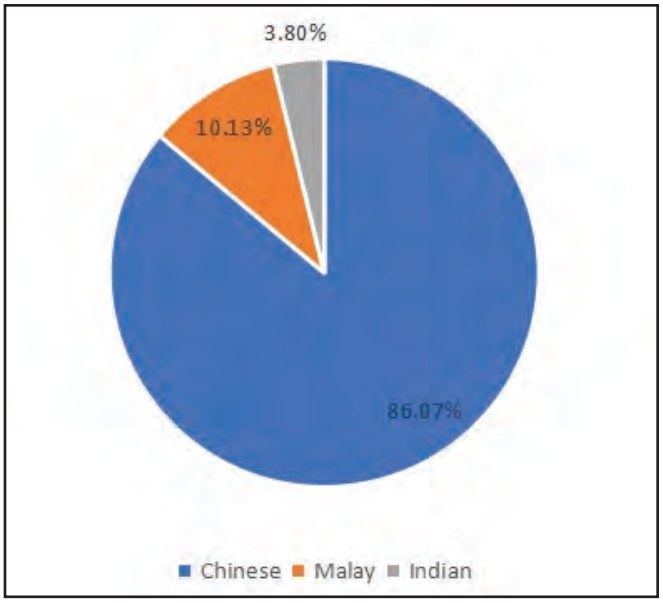

Fig. 1: Percentage of cases of NPC according to race

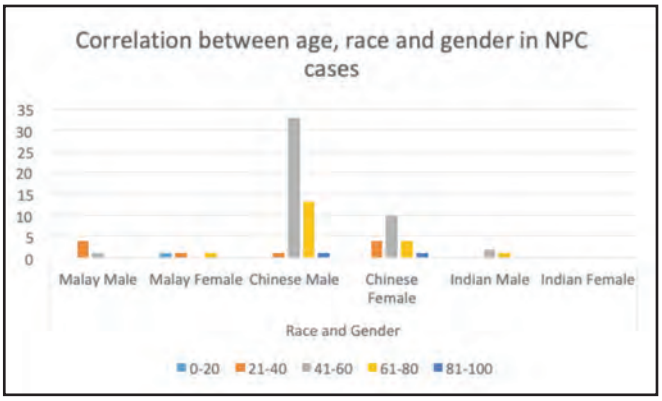

Fig. 2: Number of cases of NPC according to age group with race and gender comparison

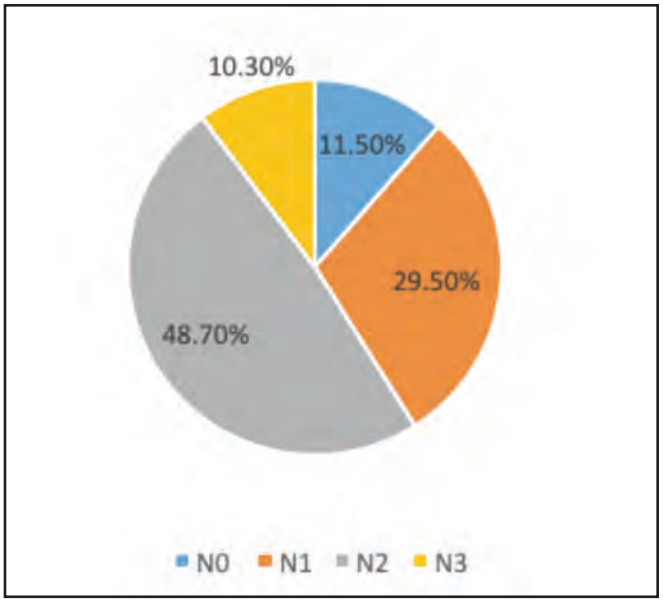

Fig. 3: Neck nodes presentation

patients (n=3) received 33 fractions of RT (Table I). All patients have concurrent chemotherapy and RT.

Tumours were staged according to TNM classification. Nine patients (11.5%) presented with no neck nodes, 23 patients (29.5%) had N1 nodes, 38 patients (48.7%) had N2 nodes while 8 patients (10.3%) had N4 nodes (Figure 3).

Twelve patients (15.4%) reported with symptoms of hypothyroidism during follow-up and their TFTs were taken. In all 12 patients, the TFT results were normal; hence, none of them was started on thyroxine. No follow-up TFT was taken for all 12 patients as results were normal and patients did not complain of further symptoms. Other 66 patients (84.6%) did not complain of symptoms of hypothyroidism, and no TFT was taken (Table II).

There is no correlation between comorbidities and hypothyroidism (p=0.9). For RT and correlation with the development of hypothyroidism, results were not significant as well (p=0.882). The number of fractions on RT given did not affect the development of hypothyroidism as p>0.05 no matter 33, 34 or 35 fractions of RT given (Table III).

DISCUSSION

It was expected up to 23% of patients develop hypothyroidism post-RT in NPC.[5] From our study, it did not show any findings of hypothyroidism as expected biochemically.

The results showed that even though up to 15.4% patients report symptoms of hypothyroidism but blood investigation revealed normal results. Patients were reported to have comorbidities like diabetes mellitus, hypertension, hyperlipidaemia and ischaemic heart disease. However, comorbidities did not have any significance on the report of symptoms of hypothyroidism. A literature search on correlation between comorbidities and hypothyroidism in NPC did not produce any findings.

Amongst our reviewed patients, the hypothyroid symptoms were subjectively reported. Later it was objectively quantified by the normal TFT in all 12 patients. As the patients have no more symptom after the normal TFT was obtained, no further blood takings or any additional investigations were carried out.

According to the Clinical Practice Guideline (CPG) on NPC published by the Ministry of Health Malaysia in 2016, thyroid function was supposed to be taken on each patient on a yearly basis.[1] This study revealed that blood was not taken in every patient but was selectively taken only in those who report symptoms of hypothyroidism. Despite only taking blood in symptomatic patients (which are more likely to have hypothyroidism), the results were normal. Thus, a revision of

CPG may be needed as taking TFT in all patients post-RT may not be suitable as prevailed in this study that even those with symptoms may have normal results. Further larger-scale studies may also be warranted to determine the need for yearly blood investigations. Asymptomatic patients may not consent to an additional blood taking as it requires an extra trip to the hospital. Another clinical audit is needed to determine the factors why blood investigations were not done in the clinical setting.

As for RT, the fraction of RT given was interpreted and showed that it did not cause the development of hypothyroidism. RT given was between 32 and 35 fractions and it depends on the stage of tumour diagnosed and the dose given on each session. As all patients in our studies were given IMRT, and it is known that the effect of IMRT which has been reported to produce lesser toxicities.[11] IMRT was also reported to produce lesser hypothyroidism compared to conventional RT.[11]

It is easy to understand that IMRT delivers full 70Gy for the gross tumour volume, GTV (actual gross tumour showed on CT/MRI) including the lymph nodes (LN) involved. A margin of 5mm from GTV, known as clinical target volume (CTV) will receive the same dose. Other CTV includes the drainage LN, will receive 60-63Gy. If GTV is a central organ, bilateral LN from level II to V will receive 60-63Gy. Other structures for example thyroid gland, pituitary or hypothalamus, are not included in the contouring. However, the radiation effect can be expected depending on how close it is to the targeted organ.

The incidence of subclinical hypothyroidism was between 24 and 50%.[7] As patients with subclinical hypothyroidism may not show symptoms, it was not known the percentage of patients that presented with subclinical hypothyroidism. However, from the results obtained, some patients presented with symptoms but the results were not hypothyroid, it can be concluded that those with subclinical hypothyroidism did not proceed to become hypothyroidism or have yet to develop hypothyroidism. About 2–5% of patients with subclinical hypothyroidism developed overt hypothyroidism.[12] No patients were started on thyroxine replacement in our study, as the TFT results taken were normal or patients were asymptomatic without blood investigation. It was assumed that those asymptomatic have normal thyroxine levels.

A study done by Wu et al. showed that the risk of clinical hypothyroidism increases after 10 years of follow-up. The incidence was up to 19.1% from the study published in 2010.[7,13] In our study, the retrospective data were collected only for patients that had NPC for the last 5 years. Thus, there was a possibility that in longer follow-up, few may present with hypothyroidism. There were no differences in blood investigation among patients who had undergone IMRT and conventional RT according to the CPG.[1] Blood investigation, according to the type of RT given, may be more practical.

If annual TFT was taken as per CPG, it is believed that patients with subclinical hypothyroidism may be detected. However, based on the results, no patients had subclinical hypothyroidism as they may have recovered without being detected. The risk of developing hypothyroidism in patients who received IMRT was lower to begin with as well.[11] Those with subclinical hypothyroidism but with a TSH less than 10mIU/L may not need treatment.[12] This has raised the further question that if an annual TFT is needed. If patients develop subclinical hypothyroidism and recover without being detected, the blood taking may just add to increase cost, resources to the hospital, and to some extent, anxiety unnecessarily.

One of the reasons why no case of hypothyroidism was detected in our study can be due to the age at diagnosis. In our study, the mean age at diagnosis was 53 years. The risk of developing hypothyroidism post-RT increase in the younger age group.[13,14] However, both studies observed the effect of hypothyroidism post-conventional RT; therefore, their study findings may not be accurately compared with our study.

CONCLUSION

Bearing in mind that radiation-induced hypothyroidism is a late toxicity that may take many years to develop, long-term follow-up is needed. If this finding is consistent with a prospective review of TFT post-RT amongst the NPC patients, the yearly thyroid function monitoring may not be needed and can only be taken depending on the type of RT received by patients. A prospective study with better control of inclusion and exclusion criteria, and longer follow-up period with TFT, is needed to demonstrate the consistency of these findings.

REFERENCES

1. Ministry of Health Malaysia. CPG Management of Nasopharyngeal Carcinoma 2016
2. Blanchard P, Lee A, Marguet S, Leclercq J, Ng WT, Ma J, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. Lancet Oncol 2015; 16(6): 645-55.
3. Razfar A, Mundi J, Grogan T, Lee S, Elashoff D, Abemayor E, et al. IMRT for head and neck cancer: cost implications. Am J Otolaryngol 2016; 37(6): 479-83.
4. Lin Z, Yang Z, He B, Wang D, Gao X, Tam SY, et al. Pattern of radiation-induced thyroid gland changes in nasopharyngeal carcinoma patients in 48 months after radiotherapy. PloS One 2018; 13(7): e0200310.
5. Luo R, Li M, Yang Z, Zhan Y, Huang B, Lu J, et al. Nomogram for radiation-induced hypothyroidism prediction in nasopharyngeal carcinoma after treatment. Br J Radiol 2017; 90(1070): 20160686.
6. Fan CY, Lin CS, Chao HL, Huang WY, Su YF, Lin KT, et al. Risk of hypothyroidism among patients with nasopharyngeal carcinoma treated with radiation therapy: a population-based cohort study. Radiother Oncol 2017; 123(3): 394-400.
7. Luo R, Wu VW, He B, Gao X, Xu Z, Wang D, et al. Development of a normal tissue complication probability (NTCP) model for radiation-induced hypothyroidism in nasopharyngeal carcinoma patients. BMC Cancer 2018; 18(1): 1-8.
8. Chan AT, Grégoire V, Lefebvre JL, Licitra L, Hui EP, Leung SF, et al. Nasopharyngeal cancer: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23: vii83-5.
9. Zhou L, Chen J, Tao CJ, Huang S, Zhang J, Shen W, et al. Hematological indexes can be used to predict the incidence of hypothyroidism in nasopharyngeal carcinoma patients after radiotherapy. Bio Med Res Int. 2020; 2020: 1-10.

10. Qiu WZ, Huang PY, Shi JL, Xia HQ, Zhao C, Cao KJ. Neoadjuvant chemotherapy plus intensity-modulated radiotherapy versus concurrent chemoradiotherapy plus adjuvant chemotherapy for the treatment of locoregionally advanced nasopharyngeal carcinoma: a retrospective controlled study. Chin J Cancer 2016; 35(1): 1-9.
11. Peng G, Wang T, Yang KY, Zhang S, Zhang T, Li Q, et al. A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. Radiother Oncol 2012; 104(3): 286-93.
12. Khandelwal D, Tandon N. Overt and subclinical hypothyroidism. Drugs 2012; 72(1): 17-33.
13. Wu YH, Wang HM, Chen HH, Lin CY, Chen EY, Fan KH, et al. Hypothyroidism after radiotherapy for nasopharyngeal cancer patients. Int J Radiat Oncol Biol Phys 2010; 76(4): 1133-9.
14. Ülger Ş, Ülger Z, Yildiz F, Özyar E. Incidence of hypothyroidism after radiotherapy for nasopharyngeal carcinoma. Med Oncol 2007; 24(1): 91-4.