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The role of Zulewski's clinical score in screening for hypothyroidism in post-radiation therapy nasopharyngeal carcinoma patients

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ABSTRACT

Background: Nasopharyngeal carcinoma (NPC) is a leading cause of cancer related death in Asia; and the fourth most common malignancy in Indonesia. Hypothyroidism is one of the most commonly overlooked radiotherapy-induced late side effect due to its gradual occurrence despite its irreversibility. Unfortunately, thyroid evaluation is not widely accessible throughout Indonesia. Therefore, it is quite important to utilize a simple and reliable surrogate tool for hypothyroidism screening. This study aims to evaluate thyroid function and to validate Zulewski's scoring system as a temporary surrogate marker for hypothyroidism in post-RT NPC patients.

Method: This is a cross-sectional study involving NPC patients between November 2015 and March 2016 at Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia. The patients had completed radiation therapy (RT) within the preceding six months. They were evaluated for signs and symptoms of hypothyroidism with Zulewski's clinical scoring system and with serological analysis of thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels.

Results: There were 97 patients in this study. 28 (28.9%) subjects experienced hypothyroidism based on the TSH and FT4 levels, with subclinical hypothyroidism (13.4%) as the most common type, followed by overt hypothyroidism (9.3%) and hypothyroxinemia (6.2%). From the subjects with hypothyroidism, 19.6% had Zulewski's clinical score <5, while 40.5% had scores ≥5. Subjects with <5 Zulewski's clinical score exhibited signs and symptoms more related to the NPC itself, while those who scored ≥5 showed signs and symptoms more closely related to hypothyroidism.

Conclusion: This study shows that hypothyroidism is commonly exhibited in NPC patients after radiotherapy (28.9%). Zulewski's clinical score of ≥5 indicates signs and symptoms more closely related to hypothyroidism.

Keywords: clinical score, nasopharyngeal carcinoma, radiation therapy, hypothyroidism

INTRODUCTION

Nasopharyngeal cancer (NPC) is a rare malignancy, with its global prevalence fewer than one case in 100,000 population. However, this disease is the leading cause of death in the Southern China region, and the fourth most common malignancy in Indonesia (cervical cancer is the first, followed by breast and skin cancers) where the incidence is 6.2 cases in 100,000 people and 12,000 new cases have been recorded annually [1].

Most NPC patients begin their treatments at advanced stage due to the late detection. Physicians are often unequipped for prompt diagnosis. Some patients have chronic non-specific symptoms mimicking upper respiratory tract infection [1]. Theoretically, NPC responds well to radiation therapy (RT) because there is active mitosis. However, multi-fraction protocols of 1.5-2 Gy may cause long-term and irreversible cumulative side effects on normal cells adjacent to the target location. Exposure of RT of the neck region leads to disruption of the hypothalamus-pituitary-thyroid axis, and eventually causes hypothyroidism–a long-term side effect brought out by the extended course of therapy [2]. In fact, radiation-induced hypothyroidism is considered the most common late, cumulative side effect, occuring in about 14-54% of NPC patients within two years after treatment completion. Delayed diagnosis of hypothyroidism may decrease quality of life and potentially cause life-threatening conditions [3].

The impact of RT on the thyroid gland was first reported in 1929, and so far, damage to the vascular and parenchymal cells

Table 1. The scoring system of Zulewski's

Evaluation	Description	Present	Absent
Signs			
Slow of movements	Observing patient while walking and sitting	1	0
Ankle reflex	Observing delayed relaxation of the ankle reflex	1	0
Coarse skin	Dermatologic examination of the hand, forearm and elbow for thickness and roughness	1	0
Periorbital puffiness	Observing periorbital swelling	1	0
Cold skin	Comparing the temperature of the hand with the examiner's	1	0
Symptoms			
Diminished sweating	Sweating in normal or warm room	1	0
Voice hoarseness	Change in speaking or singing voice	1	0
Paresthesia	Subjective sensations	1	0
Dry skin	Dryness of the skin, requiring skin moisturizing products	1	0
Constipation	Bowel habit and use of laxatives	1	0
Hearing impairment	Difficulty in hearing	1	0
Weight increase	Increase in weight	1	0

Note: A score of 6 and above is defined as hypothyroidism, while 0-2 points are considered euthyroid. A score of 3-5 is defined as intermediate

as well as autoimmune reactions has also been elaborated. Radiation dose, target thyroid volume, and prior thyroid resection have all been discovered to contribute to hypothyroidism [4]. However, the lack of accessibility makes it difficult for clinicians in resource-limited settings to evaluate for thyroid functions. This may contribute to the problem of hypothyroidism being often overlooked until the signs and symptoms cause significant impact in quality of life [5]. One way to overcome this problem is to incorporate a clinical scoring system that makes use of the commonly found symptoms and signs of hypothyroidism.

Thyroid hormone regulates epidermal homeostasis, therefore, the skin of patients with hypothyroidism is often rough and scaly, particularly on the extensor aspects of extremities due to eccrine gland hyposecretion and atrophy, which may be demonstrated by histologic examination [6]. Symptoms and signs associated with hypothyroidism are diminished perspiration, hoarseness, paresthesia, dry and scaly skin, constipation, hearing impairment, weight gain, periorbital puffiness, slower movements, and delayed relaxation of ankle reflex. In 1997, it was created a scoring system based on the Billewicz's score which was meant to reflect TSH and thyroid hormone levels [7]. These symptoms and signs are used and turned it into a convenient and simple scoring system to screen for hypothyroidism [7]. This study aims to evaluate the potential utilization of Zulewski's clinical score as a surrogate tool in the evaluation of hypothyroidism in post-RT NPC patients.

METHODS

This cross-sectional study was done from November 2015 to March 2016, at the outpatient clinics of the Hematology and Medical Oncology Division of Internal Medicine, in collaboration with the Otorhinolaryngology (ENT) Department at Dr. Cipto Mangunkusumo National General Hospital in Jakarta, Indonesia.

The study population comprised of registered NPC patients in both outpatient Hematology-Oncology and ENT clinics. Inclusion criteria were NPC patients over 18 years old who had RT within the preceding six months, whereas the exclusion criteria were previous thyroidectomy, history of thyroid diseases, and levothyroxine use. The authors assessed the hypothyroidism signs and symptoms with Zulewski's clinical score (**Table 1**). A total score higher than five indicates hypothyroidism, lower than three euthyroidism, whereas in-between intermediate [7].

Blood samples were drawn for free thyroxine (FT4) and thyroid stimulating hormone (TSH) plasma level analysis. The normal range for FT4 is 0.93-1.7 ng/dL, whereas TSH 0.27-4.20 mIU/L. The finding of elevated TSH with low FT4 indicates primary hypothyroidism due to thyroid gland disease, whereas a low TSH with low FT4 hypothyroidism due to a pituitary disorder, and low TSH with elevated FT4 hyperthyroidism. Subjects were then grouped according to their FT4 and TSH levels. Subjects with normal TSH but elevated FT4 were classified as hyperthyroxinemic, whereas those with low TSH but elevated FT4 hyperthyroid. Both hyperthyroxinemia and hyperthyroidism are categorized as thyrotoxicosis. On the other hand, patients with elevated levels of TSH but normal FT4 were classified as subclinically hypothyroid whereas those with elevated TSH but low FT4 overtly hypothyroid, and those with normal TSH and low FT4 hypothyroxinemic. These last three are categorized as hypothyroidism. Abstracted data was then compiled and analyzed with SPSS v.26. Basic characteristics of the subjects, clinical staging, chemotherapy regimen, and radiation techniques are displayed in tables.

This research was conducted in accordance with the ethical standards on human experimentation and ethical clearance for this research was granted by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia. Ethical approval number of the study was: 658/UN2.F1/ETIK/2015. Appropriate consents were obtained of each subject after providing adequate information for consent before the research. Full anonymity of patients' personal data was maintained in accordance with the declaration of Helsinki.

RESULTS

Participant Characteristics

Initially, a total of 100 patients were selected as possible respondents, however, three were excluded due to incomplete data on thyroid function evaluation. The remaining 97 patients comprised of 62 males and 35 females, while the mean age was 46.61 years, with the majority of the participants aged below 50, and the youngest, as well as the oldest patient aged 18 and 71, respectively.

Table 2. Participant characteristics

Characteristics	n=97
Age, n (%)	
<20	2 (2.1)
20-29	10 (10.3)
30-39	11 (11.3)
40-49	33 (34.0)
50-59	27 (27.8)
60-69	13 (13.4)
>70	1 (1.0)
Sex, n (%)	
Male	62 (63.9)
Female	35 (36.0)
Smoking, n (%)	
Yes	64 (66)
No	33 (34)
Radiation technique, n (%)	
IMRT	27 (27.8)
2D/3D/conventional	61 (62.9)
No data	9 (9.3)
Chemotherapy type, n (%)	
Neoadjuvant (chemosensitizer + adjuvant)	62 (64)
Chemosensitizer	16 (16.5)
Did not receive chemotherapy	6 (6.2)
Incomplete data	13 (13.4)
Chemotherapy agent, n (%)	
Platinum only	53 (53.6)
Platinum with taxan or 5FU	25 (25.8)
Taxan only	1 (1)
5FU only	1 (1)
No chemotherapy/no data	18 (18.6)

Note: IMRT: Intensity modulated radiotherapy; 2D/3D CRT: 2-dimentional conventional/3-dimentional conformal radiotherapy; & 5FU: 5-fluorouracil

Radiation Technique, Chemotherapy Type, and Regiment

The subjects received standardized therapeutic radiation of at least 60 Gy in 30-35 fractions or two Gy at each session, for five days/week, and the whole course was completed within five-seven weeks, except in cases where complications, for instance, lower hemoglobin level, infection, and fatigue occurred.

Based on **Table 2**, the radiation techniques used at the Department of Radiotherapy in Dr. Cipto Mangunkusumo Hospital include 2D/3D conformal radiotherapy (2D/3D-CRT), conventional, and intensity-modulated radiotherapy (IMRT). In addition, 62.9% of the participants were treated with 2D/3D conventional RT, 27.8% were treated with IMRT.

As depicted in **Table 2**, most patients (64%) received neoadjuvant chemotherapy. The most commonly used chemotherapeutic agent was platinum, either as monotherapy or in combination with taxane or 5-FU.

Hypothyroidism Prevalence in Nasopharyngeal Cancer Patients

Based on the FT4 and TSH levels, 28.9% of the subjects experienced hypothyroidism, the most common being subclinical hypothyroidism (13.4%) (**Table 3**). Based on Zulewski's score, there were 20 subjects (20.6%) dexperiencing hypothyroidism (**Table 3**).

Table 4 shows that the proportion of patients with hypothyroidism is higher in those evaluated more than 12 months after radiation.

Table 3. Thyroid function status of NPC patients based on biochemical markers and Zulewski score

Classification	n=97
Thyroid function by FT4 & TSH levels, n (%)	
Thyrotoxicosis	
Hyperthyroxinemia [TSH (N), FT4 (↑)]	1 (1)
Hyperthyroid [TSH (↓), FT4 (↑)]	2 (2)
Euthyroid [TSH (N), FT4(N)]	**66 (68)**
Hypothyroid	
Subclinical hypothyroid [TSH (↑), FT4 (N)]	13 (13.4)
Overt hypothoroidism [TSH (↑), FT4 (↓)]	9 (9.3)
Hypothyroxinemia [TSH (N), FT4 (↓)]	6 (6.2)
Thyroid status by Zulewski's score, n (%)	
Hypothyroidism	20 (20.6)
Intermediate	43 (44.3)
Euthyroid	34 (35.5)

Note. NPC: Nasopharyngeal carcinoma; TSH: Thyroid stimulating hormone; & FT4: Free thryoxine

Table 5 shows that nine of 20 subjects (45%) with hypothyroidism (Zulewski's score six-seven) had the appropriate TSH and FT4 levels. Furthermore, 40.5% of those who scored ≥5 also manifested hypothyroidism, based on the biochemical thyroid markers. Meanwhile, 19.6% of subjects scoring <4 had hypothyroidism, based on the FT4 and TSH levels.

Table 6 shows the number of patients with clinical symptoms and signs enlisted in the Zulewski's scoring system. Apparently, the most common findings were hearing impairment and dry skin.

DISCUSSION

In East and Southeast Asia, there are 40-50 cases of nasopharyngeal carcinoma (NPC) in every 100,000 population, higher than in Europe or the United States (<1/100,000). NPC is more common in males than females; the ratio is 2.18:1 [8]. In this study, 64% of the subjects are male. The subjects were mostly in their 40's (34%) and 50's (27.8%). These facts are in line with other studies stating that NPC patients are most commonly 30-69 years old. Smoking is a notorious risk factor for NPC and other head and neck cancers. Cigarette smoke irritates the epithelial cells in the respiratory tract, induces chronic inflammation, and ultimately causes cell metaplasia and squamous cell carcinoma. In our study, 64% of the subjects were smokers.

Radiation techniques used to administer radiotherapy for subjects in our study comprise of conventional radiotherapy, 2D/3D conformational radiotherapy (2D/3D CRT), and intensity modulated radiotherapy (IMRT). The most common radiation technique is 2D/3D CRT [9]. Previous studies had showed no significant correlation between radiation technique and incidence of hypothyroidism. It had been reported that hypothyroidism may still occur despite minimal irradiation to thyroid and pituitary glands. This might have been due to the fact that thyroid capsule and blood vessel fibrosis, as well as autoimmune reaction, contributes to the incidence of hypothyroidism [10]. The majority of patients in our study had neoadjuvant chemotherapy (64%), and the most commonly used chemotherapeutic regimen was platinum-based. Platinum was either a monotherapy (53.6%) or in combination with taxane or 5-FU (25.8%).

Table 4. Duration since receiving radiotherapy and thyroid function evaluation

Mo. after receiving RT	Thyrotoxicosis		Euthyroid	Hypothyroid			Total
	TSH (N), FT4 (↑)	TSH (↓), FT4 (↑)	TSH (N), FT4 (N)	TSH (↑), FT4 (N)	TSH (↑), FT4 (↓)	TSH (N), FT4 (↓)	
6-12	1	1	31	3	1	3	40
13-18	0	1	9	2	0	0	12
19-24	0	0	4	1	2	0	7
25-30	0	0	5	1	2	0	8
31-36	0	0	5	0	0	0	5
37-42	0	0	3	1	0	0	4
43-48	0	0	1	0	0	0	1
49-54	0	0	2	2	0	0	4
55-60	0	0	2	0	1	1	4
>60	0	0	4	3	3	2	12
Total	**1**	**2**	**66**	**13**	**9**	**6**	**97**

Note. RT: Radiotherapy; TSH: Thyroid stimulating hormone; & FT4: Free thryoxine

Table 5. Zulewski's score and thyroid function evaluation

Zulewski score	Thyrotoxicosis		Euthyroid	Hypothyroid			Total
	TSH (N), FT4 (H)	TSH (L), FT4 (H)	TSH (N), FT4 (N)	TSH (H), FT4 (N)	TSH (↑), FT4 (↓)	TSH (N), FT4 (H)	
0	0	0	7	1	1	0	9
1	1	0	9	2	2	2	16
2	0	1	8	0	0	0	9
3	0	0	10	1	1	0	12
4	0	0	9	0	1	0	10
5	0	0	13	4	2	2	21
6	0	1	5	4	0	0	10
7	0	0	5	1	2	2	10
Total	**1**	**2**	**66**	**13**	**9**	**6**	**97**

Note. RT: Radiotherapy; TSH: Thyroid stimulating hormone; & FT4: Free thryoxine

Table 6. Zulewski's clinical signs and symptoms and thyroid function evaluation

Zulewski signs & symptoms	Thyrotoxicosis		Euthyroid	Hypothyroid			Total
	TSH (N), FT4 (H)	TSH (L), FT4 (H)	TSH (N), FT4 (N)	TSH (H), FT4 (N)	TSH (H), FT4 (L)	TSH (N), FT4 (L)	
SoM	0	1	1	0	0	1	3
Delayed ankle reflex	0	0	0	0	0	0	0
Coarse skin	0	0	18	4	3	2	27
Periorbital swelling	0	1	6	2	2	0	11
Cold skin	0	1	5	0	0	0	6
DP	0	0	27	7	4	4	42
Hoarse voice	0	0	28	**9**	4	4	45
Paresthesia	0	1	25	8	3	4	41
Dry Skin	0	1	**32**	7	**6**	4	50
Constipation	0	0	13	3	1	0	17
Hearing impairment	1	2	**38**	8	**6**	3	58
Weight increase	0	1	28	8	4	4	45

Note. RT: Radiotherapy; TSH: Thyroid stimulating hormone; FT4: Free thyroxine; SoM: Slowness of movements; & DP: Diminished prespiration

Thyroid dysfunction is a commonly underestimated radiation-induced side effect, and primary hypothyroidism seems to be the most common long-term side effect; its incidence is 20-30% [11]. Our study found that, based on the gold standard of measuring TSH and FT4 levels, approximately 15.5% of the study subjects had low FT4 levels. The mean FT4 level was 3.66, and the mean TSH level 1.17.

Furthermore, based on the Zulewski's scoring system, we found that 20.6% of the subjects experienced hypothyroidism. The incidence of hypothyroidism differed from previous studies summarized by [12], which concluded that the incidence of clinical and subclinical hypothyroidism in post-RT head and neck cancer patients ranged between 2-92%. It was conducted a prospective study comparing TSH and FT4 levels of NPC patients before and after radiotherapy [13]. All patients had had normal thyroid function before radiotherapy, but it was reported that there was a 23.1% decrease in thyroid hormone levels in NPC patients after receiving radiation therapy [13]. The reported percentage is lower than our finding 28.9% of the subjects had hypothyroidism.

Hypothyroidism may occur as early as within three months after radiation, with peak incidence within two-three years post-radiation. Both NCCN and ESMO recommend that NPC patients during and post-radiation undergo routine thyroid function evaluation. However, the clinical practice guidelines in Indonesia have yet to include thyroid function evaluation in the routine follow-up protocol. In particularly resource-limited areas, lack of laboratory access has made it difficult for clinicians to evaluate hypothyroidism. A simple tool like Zulewski's clinical score will aid clinicians in determining hypothyroidism.

It was stated that 12 months post-radiation is the optimal time for hypothyroidism evaluation [14]. It has been reported that post-radiation thyroid dysfunction is progressive and irreversible. Duration of radiation therapy is also correlated to incidence of hypothyroidism.

Billewics first described signs and symptoms of hypothyroidsm in 1969. These include lethargy, somnolence, weight gain, behavioral change, constipation, change in voice, paresthesiae, muscular pains, dyspnea, cold intolerance, reduced appetite, poor memory, decreased sweating, obstructive sleep apnea, hearing loss, facial puffiness, pallor, delayed reflexes, slow movements, hairfall, pericardial effusion, enlarged tongue, galactorrhea (in female), xanthelasma, coarse skin. These signs and symptoms were then correlated to the thyroid function tests by Zulewski, who categorized the patients into hypothyroid (score >5), intermediate (three-five) and euthyroid (<3). In general, the most common signs or symptoms among NPC patients in our study were hearing loss, dry skin, then followed by change in voice and weight gain.

In this research, 20 subjects scored ≥6 and among them, there were nine (45%) with hypothyroidism; furthermore, of 43 subjects scoring three-five, there were 11 (25.6%) with hypothyroidism, whereas of those scoring 0-2, there were eight (23.5%) with hypothyroidism, based on the biochemical markers for thyroid function (TSH and FT4). In this research, we found that 70.6% of patients with hypothyroidism scored ≥3. Therefore, even though further analysis of thyroid function using biochemical markers is a must when patients were screened for hypothyroidism, we should not disregard the possibility that those scoring <6 might also have hypothyroidism.

Some signs and symptoms in the Zulewski's clinical score are closely related to hypothyroidism—weight gain, coarse skin, and decreased prespiration. Thyroid hormone regulates basal metabolism, thermogenesis and plays a significant role in lipid, as well as glucose metabolism, food intake, and fat oxidation [15]. Therefore, thyroid dysfunction is associated with changes in body weight and composition. Hypothyroidism leads to reduced thermogenesis and decreases metabolic rate, as well as to higher body mass index (BMI) and obesity prevalence [16,17]. In 2011, researchers reviewed the function of thyroid hormone as an important regulator of epidermal homeostasis [6]. In hypothyroidism, the skin is rough and scaly from decreased eccrine gland secretion, especially on the extensor extremities. Dryness is also notable on the palms and soles, and histological evaluation detects epidermal thinning and hyperkeratosis. The dermal layer tends to be pale due to changes in dermal mucopolysaccharides and water content. In addition, increased dermal carotene may appear as a prominent yellow hue on the palms, soles, and nasolabial folds [6]. A histological study on hypothyroidism discovered increased hyaluronic acid level in the hypothyroid dermis [18]. Therefore, in patients with these signs and symptoms, even though their Zulewski clinical score is <5, we recommend heightened awareness that a patient may still have hypothyroidism. Further appropriate examination, if possible, should be performed.

There are other signs and symptoms accounted in Zulewski's scoring tool, but those are not exclusive to hypothyroidism. Post-RT NPC patients frequently presents with some of the same NPC signs and symptoms, with or without hypothyroidism, for example: hearing loss, hoarse voice, paresthesia, and periorbital puffiness. Hearing impairment, specifically sudden sensorineural hearing loss (SNHL), is present in congenital hypothyroidism or in autoimmune-related thyroid dysfunction [19]. Thyroid dysfunction has also been associated with hypercoagulability and venous thrombosis. Hearing impairment occurs when this condition affects cochlear circulation [19]. Therefore, in this research, subjects with hearing only (Zulewski's score=1) could have had that complaint due to radiation therapy and/or the NPC itself [20], without induction to hypothyroidism. Several studies have recognized that SNHL is an imminent adverse effect of radiation developing within 6-24 months after irradiation [20]. The underlying mechanism is reduced capillary perfusion and endotheliocyte degradation, direct effect to the cells of Corti organ, stria vascularis degeneration and atrophy as well as atrophy of the cochlear nerves and spiral ganglion cells [20-22].

Hypothyroidism may lead to hoarse voice, vocal range changes, and vocal fatigue. The voice change is caused by fluid accumulation in the surrounding tissue of the vocal cords, noticeably in overt hypothyroidism [23]. A similar underlying mechanism could explain periorbital puffiness: fluid retention in the connective tissue surrounding the eyes [22-25]. Furthermore, various neurological changes resulting from hormone dysregulation, there may be both central and peripheral neuropathies, including delayed reflexes, numbness, and paresthesia [26].

In our study, some of the subjects did not have documentation for TSH and FT4 levels. We suggest that when examining an NPC patient with Zulewski's clinical score 0-5, a clinician should suspect that certain signs and symptoms could have been incurred by NPC itself, or as direct, delayed effects of RT. Another common complaint from NPC patients is constipation. In overt hypothyroidism, constipation may be brought up by decreased metabolism rate, along with fluid retention, which alters intestinal contractility [26, 27]. However, constipation may also be found in patients with malignancy, especially head and neck cancers, in which there may not only be gastrointestinal disorder, but also troublesome swallowing causing poor intake.

The study [28] in 2017 on 14,893 NPC patients in Taiwan demonstrated higher risks for hypothyroidism in NPC than head and neck cancer patients. Hypothyroidism is definitely a serious adverse effect of radiation therapy in NPC patients [28] TSH and FT4 levels have been the gold standard for hypothyroidism diagnosis, but they are infrequently unaffordable and inaccesible. The adverse effects of radiation therapy should be promptly detected in primary care setting to conserve the patients' quality of life. This study provides data that Zulewski's clinical score may aid in the diagnosis of hypothyroidism when thyroid function assay is inaccessible [29, 30]. To our knowledge, there have not been extensive studies addressing the use of Zulewski's clinical score as a surrogate tool for hypothyroidism screening in post-RT NPC patients. Our study has attempted to gather data necessary in determining the risk of developing post-RT hypothyroidism.

CONCLUSION

Hypothyroidism commonly occurs in post-RT NPC patients. In places where thyroid function assay is unavailable, Zulewski's clinical scoring system may be utilized as a surrogate tool.

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Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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