Prevalence of Hypothyroidism Following Radiotherapy of Nasopharyngeal Cancer Patients in Srinagarind Hospital between 1994 and 2007

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Abstract

Objectives : To investigate the frequency and severity of hypothyroidism following external beam radiotherapy to head and neck region in the treatment of nasopharyngeal cancer and to evaluate factors related with prevalence of hypothyroidism.

Methods and Materials: Patients with non-metastatic nasopharyngeal cancer treated with radiotherapy to head and neck region in Srinagarind hospital between January 1994 and December 2007. These patients were evaluated thyroid function (TSH and FT4) and symptoms of hypothyroidism when they came to be followed up after complete radiotherapy. Then the patient's data were reviewed regarding to age, gender, image findings, staging, histopathology, radiation fields, radiation dose, chemotherapy and clinical status.

Results : Eighty five nasopharygeal cancer patients were enrolled to evaluate thyroid function. Ten patients (12%) have developed hypothyroidism, five of them were classified as central hypothyroidism, and five were primary hypothyroidism. Seven patients had subclinical hypothyroidism and three patients had clinical hypothyroidism. The latent period of hypothyroidism ranged between 5 months to 15 years after complete radiotherapy. In clinical hypothyroid patients, clinical presentations were not so obvious. From statistical analyses, only latency of post-radiation time showed significant influence to development of primary hypothyroidism and adjuvant chemotherapy influenced the development of central hypothyroidism.

Conclusion : The prevalence of hypothyroidism in our study is 12% at 15years after radiotherapy and most of the hypothyroid patients were subclinical hypothyroidism. So, we recommend thyroid function test to be a routine follow-up check for the patients who had been treated by radiotherapy to head and neck region.

Keywords : Hypothyroidism, Nasopharyngeal cancer, Radiotherapy

Nasopharyngeal carcinoma (NPC) is a common cancer in Southeast Asia. In Thailand, the highest incidence is found in Chiang Mai province, especially in hilltribers, which is estimated to be about 14% of their population and the incidence of nasopharyngeal cancer is common in the North East of Thailand. The primary treatment modality for NPC is radiation therapy (RT). The radiation fields usually cover both thyroid and pituitary glands. So, primary and central hypothyroidism could happen after radiotherapy.

Although the incidence of radiation induced thyroid dysfunction reported in several studies varied so much between 3-92 %. In Thailand, the incidence and prevalence of radiation induced hypothyroidism and time onset were not much reported. Furthermore, the significant risk factors of radiation induced hypothyroidism are unclear.

MATERIAL AND METHOD

This study was conducted prospectively in the patients with non- metastatic nasopharyngeal cancer who were treated by radiation therapy in Division of Radiotherapy, Srinagarind Hospital between January 1994 and December 2007. There were 1,164 patients with nasopharyngeal cancer whom had been treated. The number of evaluable sample size was calculated by WINPEPI program.[14]

The inclusion criteria were : 1) Patients with non-metastatic nasopharyngeal cancer who had been treated by radiation therapy in Division of Radiotherapy, Srinagarind Hospital between 3 January, 1994 and 31 December, 2007 ; 2) patients must have no familial history of thyroid diseases ; 3) No history of previous irradiation at head and neck and thyroid surgery; 4) patients must have written informed consent before being enrolled into the study.

The exclusion criteria were 1) patients who did not have sufficient data records; 2) patients with previous history of thyroid disorder.

The Duration of study is from October 2008 to January 2009.

When the nasopharyngeal cancer patients with post radiotherapy came to be followed up in our Radiation Oncology Unit will routinely be examined for detection of residual and/or recurrent tumor and treatment-related complications. Clinical signs and symptoms of hypothyroidism were also evaluated. Thyroid function test is one of routine check will be ordered following standard guideline whenever the patients agree to participate in the study and had given informed consent.

Then the patient data was reviewed regarding to age, sex, image findings, staging, histopathology, radiation fields, radiation dose, clinical status and thyroid function test.

In this study, we want to find out types and severity of hypothyroidism. So, we decided to check thyroid stimulating hormone (TSH) and free thyroxin (FT4). All blood samples were tested with radioimmunoassay method by same laboratory. The normal value of TSH in serum is 0.50-5.10 μIU/ml and free thyroxin is 0.7-1.8 ng/dl. This normal value is the standard value used in Srinakarind hospital.

Clinical hypothyroidism and subclinical hypothyroidism were defined by combination of elevated TSH and decreased of FT4 level correlated with clinical signs and symptoms. Primary and central hypothyroidism were categorized as classified by combined TSH and FT4 level in table 1.

The definition of primary hypothyroidism (PH) is the hypofunction of thyroid gland primarily caused by thyroid gland itself, and central hypothyroidism (CH) is the hypofunction of thyroid gland resulting from damage to the pituitary, hypothalamus or hypothalamic-pituitary portal system.

We calculated the latency period of developing hypothyroidism from the date of completed radiotherapy to the date of abnormal thyroid function were detected. The percentage of patients who were identified to have thyroid hypofunction from all the enrolled patients was assumed to be the prevalence of hypothyroidism in our study. In patients who had repeated radiotherapy, the latency period were calculated from the date of complete first radiotherapy course.

Treatment considerations :

Because there was heterogeneity of staging data, radiation techniques, treatment parameters, field arrangements, beam energies, total doses, and fraction sizes. So, we had to recalculate the same bioequivalent radiation dose to primary tumor and neck nodes.

Table 1 : Classification of hypothyroidism

Type	Serum FT4	Serum TSH	Clinical manifestations
Subclinical PH	Normal	High	Vague symptoms/no symptoms
Clinical PH	Low	High	Symptoms present
Subclinical CH	Normal	Low	Vague symptoms/no symptoms
Clinical CH	Low	Low	Symptoms present

NB : PH = primary hypothyroidism, CH = central hypothyroidism

Radiation dose:

The different dose-time fractionation of radiotherapy were recalculated to be bioequivalent to conventional fractionation (2Gy per fraction, five times per week).

The Withers formula[17] was used to convert a total dose D delivered with dose per fraction d into the isoeffective dose of 2 Gy/fraction.

The α/β ratio of thyroid gland was reviewed from different resources. Many references recommend the α/β ratio of thyroid gland as 3[18]. Total radiation dose in all patients were recalculated to bioequivalent dose of 2 Gy per fraction for comparison the effect of radiation dose in each patients.

$$EQD2 = D\left[\frac{d+(\frac{a}{b})}{2+(\frac{a}{b})}\right]$$

Average radiation dose at neck

Due to varying radiation techniques and radiation dose on each side of neck, we decided to use average dose in the comparison analysis.

Restaging

Since, the definition of staging system of nasopharyngeal cancer had been changed in the year 1992, 1998 and 2002. So, we had to restage all the enrolled patients with nasopharyngeal cancer to AJCC system 2002.

Statistic analysis

The factors related to hypothyroidism following radiotherapy were evaluated by program SPSS v.16

Discrete variables were gender, staging, concurrent chemoradiotherapy, adjuvant chemoradiotherapy, radiation machines, re-irradiation at head and neck, brachytherapy and radiation technique at the last follow up were described by proportions.

Continuous variables were age at diagnosis, latency of post radiation time, radiation dose at neck and radiation dose at nasopharynx , were described by mean, standard deviation or median.

Multivariate binary logistic analysis was used to evaluate factor variables in respect to prevalence hypothyroidism.

RESULTS

In this study 85 patients with nasopharyngeal carcinoma who received radiation therapy to the head and neck region were evaluated. The mean age at diagnosis was 52.3 yr (median: 52 years, range: 25–78 years) and 54 patients were male (63.5%). The mean latency period of developing hypothyroism was 3.4 years (median: 2years, range: 0.4 -15 years)

The mean radiation dose at nasopharynx applied were 68.5 Gy (52–74.5 Gy) The mean radiation dose at neck applied were 60.5 Gy(48.4-70Gy) for positive neck node patients and were 56.6Gy (40-70Gy) in negative neck node patients.Some demographic properties and stages of the patients according to the AJCC2002 staging system are shown in Table 2.

All patients were treated with external beam radiotherapy with and without chemotherapy. Twenty two patients (25.9%) were treated with concurrent chemoradiotherapy and twelve patients (14.1%) received adjuvant chemotherapy after completed radiation.

Among of these patients, there were 17 patients who had local recurrence and have to be retreated with EBRT at nasopharynx. Three of them had primary hypothyroidism and two had central hypothyroidism.

Table 2 : Characteristics of the Patients

Some Characteristics of the Patients	N(%)	
Gender		
Male	54(63.5%)	
Female	31(36.5%)	
Stage		
Stage I	4(4.7%)	
Stage IIA	2(2.3%)	
Stage IIB	13(15.3%)	
Stage III	23(27.1%)	
Stage IVA	23(27.1%)	
Stage IVB	20(23.5%)	
	Mean	Range
Age at diagnosis (years)	52.3	(25-78)
Latency period of developing hypothyroidism (years)	3.4	(0.4-15)

Table 3 : Status of thyroid function

Thyroid function status	number of patients
Euthyroidism	75
Hypothyroidism	10
Clinical primary hypothyroidism	3
Subclinical primary hypothyroidism	2
Clinical central hypothyroidism	0
Subclinical central hypothyroidism	5

Prevalence of hypothyroidism following radiotherapy :

In the enrolled 85 patients with nasopharyngeal cancer, ten patients (12%) have developed hypothyroidism. Five patients were central hypothyroidism, and five were primary hypothyroidism. Seven patients were subclinical hypothyroidism and 3 patients were clinical hypothyroidism. Number of patients in each group is presented in table 3.

We had observed subclinical hypothyroidism more than clinical hypothyroidism. In clinical hypothyroid patients, we did not detect any patients with obvious clinical hypothyroidism. Only one patient with clinical hypothyroidism experienced symptom of fatigue without other symptoms.

Table 4.1 and table 4.2 shows factors related to hypothyroidism following radiotherapy. The relative significance of variables such as age, gender, post radiation time, radiation dose, concurrent chemoradiotherapy, adjuvant chemoradiotherpy, etc. were analyzed by univariate and multivariate analysis using Cox regression analysis.

From statistical analyses, only post-radiation time significantly related to development of primary hypothyroidism and adjuvant chemotherapy significantly related to development of central hypothyroidism.

From univariate analysis, gender and adjuvant chemotherapy seemed to relate to development of central hypothyroidism. However, multivariate analysis showed that adjuvant chemotherapy is the only factor statistically related to development of central hypothyroidism.

DISCUSSION

The prevalence of hypothyroidism at 15 years after radiation treatment in our study is 12%. Our prevalence is different from study of Ulger et al.[5], which reported prevalence of 14% of hypothyroidism after radiotherapy in nasopharyngeal cancer at 7 years. Y. Wu et al [9] reported the prevalence of hypothyroidism after radiotherapy for nasopharyngeal cancer patients with 4.9% at 3 year, 7.9 % at 5 year and 49.7% at 10 year.

Although hypothyroidism following radiotherapy is generally developed at 2–3 years after completion of the treatment. But there was a report of early hypothyroidism at 3 months after radiotherapy [19]. In contrast, late occurrences of hypothyroidism can occurred as late as 20 yr after completion of the therapy [15],[20] ,[21]. In our study, we had observed an early hypothyroidism occurring at 5 month after radiotherapy. According to data of Nishiyama K et al.[19] they reported hypothyroidism detected at 3 months after radiotherapy. However, half of the hypothyroidism occurs in the first 5 years after the therapy, with the peak latency period of 2–3 years.

We separated analyses for primary and central hypothyroidism by two reasons. First, radiotherapy is a local treatment which should effect mostly on organs of irradiated such as nasopharynx which located near pituitary gland should contributed to development of central hypothyroidism. Likewise, irradiation at neck should contributed to development of primary hypothyroidism. Second, to find out significant factors related to primary hypothyroidism and central hypothyroidism.

In our study, median latency period of primary hypothyroidism was 6 years and central hypothyroidism was 1 year. Central hypothyroidism has been observed more early than primary hypothyroidism. This result is different from Bhandare N. et al.[22] which reported median latency period of 3.1 years for primary hypothyroidism and 4.8 years for central hypothyroidism. The reasons of discordant of different studies may be due to different radiation techniques and radiation dose at each region.

From our data analysis, mean radiation doses at nasopharynx was 68.5 Gy, and 60.5 Gy for positive neck nodes and 56.6Gy for negative neck node patients. Higher radiation dose to nasopharynx /or pituitary gland contributed to more occurrence of central hypothyroidism than primary hypothyroidism and shorter latency period to development of hypothyroidism.

Hypothyroidism is a frequent condition in a random population sample, with a prevalence of about 2% in females[23]. It is more common in women than in men [23], and the prevalence increases with age [24]. Previous studies on the risk of hypothyroidism after neck irradiation has shown that hypothyroidism is more frequent in women than in men [25]. However, our study showed no significant correlation between age nor sex with hypothyroidism.

The clinical manifestations of central hypothyroidism are similar to those of primary hypothyroid. The most common symptoms of hypothyroidism include fatigue, cold intolerance, muscle cramp, and weight gain. The manifestations of hypothyroidism include depression, slow mentation, pericardial and pleural effusions, and a decrease in gastrointestinal tract motility. Decreased wound healing, acceleration of atherosclerosis, hypercholesterolemia, and an increased risk of developing thyroid cancer have been associated with head-and-neck irradiation.[22] In our study we did not detect any patients with obvious clinical presentation of hypothyroidism. Only one patient with clinical primary hypothyroidism presented with fatigue without other symptoms.

From statistical analyses, post-radiation time significantly related to development of primary hypothyroidism. And radiation induced hypothyroidism is a late radiation complication, so, we can expect the longer the post radiation time the more the prevalence of radiation induced hypothyroidism. According to the standard treatment guideline of nasopharyngeal cancer, concurrent chemoradiotherapy and adjuvant chemotherapy usually practiced for locally advanced cases which can improve survival rate[17], [26]. So,the longer the survival the more the incidence of radiation induced hypothyroidism will occur.

The limitation of our study was no baseline investigation of thyroid function before radiotherapy. So, we did not know whether the patients had hypothyroidism before treatment or not. Our study was retrospective in nature, we had to approximate the time specific for the event of hypothyroidism due to lacking of consistency and frequency of endocrine evaluations. And some patients lost to be followed up who could contribute to underestimation of the prevalence of hormone deficiency. Our study, however, need long-term follow up, since the prevalence of hypothyroidism increases with time after completed radiation therapy. Also baseline study of thyroid function is a matter to be considered.

Monitoring complications of cancer treatment is essential in the follow-up procedure for all cancer survivors. Radiation-induced hypothyroidism, although the mechanism is not fully understood, is a well known side effect that can be easily treated with hormone replacement therapy. Tests for detection of thyroid hypofunction should therefore be included in the evaluation of patients treated with radiotherapy at head and neck region. There is no common consensus for following thyroid function test. But it seems to be benefited if we start to check thyroid function as early as 6 months following completed radiotherapy for early detection of hypothyroidism.

Table 4.1 : Univariate analysis of patients with primary and central hypothyroidism

Variables	Odds ratio	95% CI	P value
Primary hypothyroid (n=5)			
Gender	1.17	(0.19, 7.43)	0.87
Staging	0.32	(0.02, 0.09)	0.03*
Age at diagnosis	0.834	(0.74, 0.90)	0.91
Latency of post radiation time	0.012	(∞,0.035)	<0.0001*
Radiation machine	1.65	(0.26, 10.55)	0.59
Radiation dose at neck	0.93	(0.88,0.98)	0.99
Re-irradiation	3.24	(0.49,21.20)	0.20
Midline shielding at lower neck	2.43	(0.26,22.75)	0.42
Brachytherapy at neck node	0.94	(0.89,1.00)	0.57
CCRT	0.92	(0.86,0.99)	0.18
Adjuvant CMT	0.93	(0.88,0.99)	0.37
Central hypothyroidism (n=5)			
Gender	0.91	(0.83, 0.99)	0.08
Staging	0.44	(0.34, 0.55)	0.04
Age at diagnosis	0.84	(0.16, 4.49)	0.84
Latency of post radiation time	0.07	(0.02, 0.13)	0.99
Radiation machine	3.96	(0.62, 25.28)	0.12
Radiation dose nasopharynx	0.11	(0.04, 0.17)	0.03*
ICRT at nasopharynx	6.41	(0.54, 76.34)	0.09
Re-irradiation	3.14	(0.48,20.60)	0.21
CCRT	5.17	(0.80,33.34)	0.06
Adjuvant CMT	13.50	(1.96,93.246)	0.001*

Abbreviations : RT=radiotherapy, CCRT=concurrent chemoradiotherapy, CMT=chemotherapy,
*Statistically significant, Pearson Qui-square test - p value is considered significant if ≤0.05.

Table 4.2 : Multivariate analysis of patients with primary and central hypothyroidism

Variables	Odds ratio	95% CI	P value
Primary hypothyroid (n=5)			
Gender	0.50	(0.03, 8.67)	0.64
Staging	1.79	(0.03, 93.88)	0.77
Age at diagnosis	0.95	(0.86, 1.05)	0.31
Latency of post radiation time	1.58	(1.12, 2.23)	0.01*
Radiation machine	0.04	(0.001-1.55)	0.08
Radiation dose at neck	1.00	(0.99, 1.01)	0.49
Re-irradiation	4.55	(0.32, 65.63)	0.27
Midline shielding at lower neck	0.18	(0.01,2.76)	0.22
Brachytherapy at neck	0.00	(0,∞)	1.00
CCRT	0.00	(0,∞)	1.00
Adjuvant CMT	0.00	(0,∞)	1.00
Positive neck node	0.22	(0.03, 2.01)	0.18
Central hypothyroidism (n=5)			
Gender	9.05	(0,∞)	1.00
Staging	13.40	(0.73, 247.69)	0.08
Age at diagnosis	0.96	(0.85,1.09)	0.54
Latency of post radiation time	0.25	(0.04, 1.47)	0.13
Radiation machine	1.50	(0.13, 17.29)	0.75
Radiation dose nasopharynx	1.00	(0.99,1.02)	0.62
Brachytherapy at nasopharynx	3.05	(0.07,142.45)	0.57
Re-irradiation	7.88	(0.66, 94.2)	0.10
CCRT	0.00	(0,∞)	1.00
Adjuvant CMT	25.13	(2.33,271.19)	0.01*

Abbreviations : RT=radiotherapy: other abbreviation as in table 5.1.
*Statistically significant.

CONCLUSION

From our preliminary data, patients with nasopharyngeal cancer, both treated by radiotherapy alone or combination with chemotherapy could develop hypothyroidism. So, we recommend to evaluate thyroid function in every patients with nasopharyngeal cancer who were treated by radiation for long term follow-up. Our recommendations are as followed:

1) Thyroid function should be assessed at 6 month after treatment and subsequently every 6-12 month intervals for long term follow-up.

2) Patients who already develop clinical hypothyroidism must be treated by thyroxine replacement as early as possible to prevent associated morbidity.

3) Patients with subclinical hypothyroidism should be commenced on thyroxine to bring their thyroid stimulating hormone into normal range. Because, these patients will eventually progress to clinical hypothyorism.

The results of our study provide knowledge about prevalence and patterns of hypothyroidism in patients who received radiotherapy at head and neck region. These enable us to give more defined recommendations as listed above into our routine clinical practice.

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