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Original Article

Abnormal Hormonal Secretions Post Radiotherapy for Nasopharyngeal Cancer*

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Abstract

Objective: To investigate the incidence of abnormal hormone level in the nasopharyngeal cancer patient who received radiotherapy.

Materials and Methods: We have studied the incidence of abnormal function of adrenal and thyroid gland in patients with nasopharyngeal cancer who received radiotherapy at Division of Therapeutic Radiology and Oncology, Faculty of Medicine, Chiang Mai University. There were 60 patients, 36 male, 24 female. All patients were examined clinically and laboratory for signs of abnormal thyroid function. All patients had blood tests to determine the free hormone from thyroid and pituitary glands (TSH, FT3, FT4) and adrenal glands by using insulin tolerance test then reconfirm by using pituitary hormone injection intravenously to check the function of adrenal gland (ACTH Stimulation test).

Results: The result revealed abnormal function of adrenal glands 13.3%, abnormal thyroid function 65% in which 38.3% come from abnormality of the pituitary gland and hypothalamus (central hypothyroid) and primary hypothyroidism in 18.3%. Subclinical hyperthyroid was found in 8.3%. But we were not able to differentiate signs and symptoms of the patients with adrenal insufficiency and hypothyroidism from patients who have normal level of hormone.

Conclusion: This study found high incidence of abnormal hormone level in the nasopharyngeal cancer patient who received radiotherapy.

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Introduction

Nasopharyngeal carcinoma is a common cancer in Southern China and Southeast Asia. In Thailand nasopharyngeal cancer is number 8 cancer found in male and it also one of the most common head and neck cancer. The standardized incidence rate of nasopharyngeal cancer in Thailand is 2.8 and 1.4 per 100,000 in males and in females respectively. Chiang Mai has the highest incidence rate of 3.8 for males and 1.6 for females.[1,2] The treatment for NPC is mainly radiotherapy or combined radiochemotherapy. The effect of radiotherapy to the normal tissue especially the thyroid gland, pituitary gland including hypothalamus may give rise to decrease hormonal level. So far we do not have the incidence of abnormal level of the hormonal in NPC patients who were treated with radiotherapy in Thailand, so this report may helps us understand the situation in this group of patients.

Materials and Methods

We have followed the patients who were treated with radiotherapy in Section of Therapeutic Radiology and Oncology, Faculty of medicine, Chiang Mai University, from 1984-1995. There were 60 patients. 36 male, 24 female age range 19-63 years, the median age for male was 47.1±11.3, and 39.9±13.2 for female.

There were 13 patient who had base of skull involvement but there was no pituitary gland involvement in all 60 patients. Last follow up C.T. scan showed no evidence of recurrent or metastases. All patients has no retreatment by radiotherapy or chemotherapy two years before the tests. Patients with convulsion, abnormality of the vessel in the brain, cardio vascular disease and other serious illness were excluded from the study.

Any patients who received the medication that may effect the testing of the hormone were asked to stop the medication for at least one month. All patients were tested for thyroid and adrenal gland functions except for one patient who did not have Insulin tolerance test due to the problem with venepuncture so ACTH stimulation was used in this patient.

All patient received one course of radiotherapy except one patient who receive first course of RT in 1987 and second course of RT for relapse in 1994.

The patients were staged according to TNM/AJCC/UICC 1986 classification, there were 2 patient in stage I, 8 patients in stage III and 50 patients in stage IV.

Radiotherapy Technique

All patients received two paralled opposing fields using Cobalt-60 or 6MV Linear Accelerator, 200 cGy/day, 5 days/week, the radiation dose was from 62-72 Gy. The treatment field covered the pituitary area and sphenoid sinuses at the upper border in all patients with stage IV, the anterior border covered the posterior 2/3 of the maxillary sinuses and in the case with anterior extension of the tumor to the nasal cavity, the field also extended to over this area, the posterior border cover the area of post auricular nodal area, the lower part of the field was at the mid part of the neck or to cover the enlarged lymphnodes area. The lower neck and supraclavicular areas were treated with anterior single field with central shielding.

After 40-44 Gy the radiation field was reduced to avoid the spinal cord. Booster dose to the enlarged lymph nodes or the area behind the cord were given by electron. The radiation dose was 50

Gy for all microscopic area, large nodes or gross tumor received higher dose to 66-70 Gy. After 60 Gy, the field was further reduced to include only nasopharyngeal area to 66-70 Gy. The anterior lower neck and supraclavicular field received 50 Gy.

Hormonal Analysis

Adrenal and Thyroid function tests were done in all patients, the tests were done 8.00AM after nothing by month at least 8 hours before the test.

Thyroid function tests

Serum thyrotropin (TSH), free triiodothyromine (FT_3) and free thyroxine (FT_4) were done by chemi-luminescent (ECLIA) by using Elecsys 1010 machine (Berringer Manheim)

The normal level for Northern Thai is

TSH = 0.32 - 4.38 /ml

FT_4 = 1.03 - 1.77 mg/dl

FT_3 = 0.22 - 0.40 mg/dl

Adrenal gland function test

Adrenal gland function test was done by insulin tolerance test (ITT), using short acting human insulin injection (Humulin - R, Eli Lilly Co.) 0.1 unit/kg then the blood was drawn for plasma glucose and cortisol at 0, 30, 60, and 90 minutes after insulin injection or more often if the patients developed any abnormal symptoms.

This test was considered completed when the level of blood sugar ≤40 mg%, if this level could not be achieve then higher dose of Insulin 0.15 - 0.2 unit/mg was given until the blood sugar level was at the above desired level. The normal ITT test was the level of serum cortisol ≥20 μ/dl during the hypoglycemia.

ACTH stimulation test was done by intravenous injection of the ACTH then the blood was drawn for cortisol level at 30 and 60 minutes, the normal value was the same as ITT.

After the blood was taken from the patients, it was immediately centrifuged and kept at -20°C, the serum cortisol was done by enzyme immuno-assay (EIA)

Statistical Method

The value of the tests were analyzed using mean and standard deviation, student's T-test was used to test the hypothesis. chi-squares and Fisher exact test were used to test the difference. The significant level is less than 0.05.

Results

The number of patients in this study were 36 males and 24 females. Mean age for male was 47.1±11.3 years and 39.9±13.2 years for female, the mean radiation dose was 70.7±5.4 Gy. Disease free interval was 55.2±34.5 months (table 1). Hypo-thyroidism occurred in 34 out of 60 patient (56.6%), 11/34 (18.3%) primary hypothyroidism, 23/60 (38.8) had central hypothyroidism and subclinical hypo-thyroidism in 5/60 (8.3%; table 3).

Adrenal insufficiency occurred in 8/60 (13.3%) patients. These patients had combined thyroid and adrenal insufficiency. One patient had hyperthyroi-dism (Table 4, 5) revealed no difference in age and radiation dose in the abnormality of the function of thyroid and adrenal glands. But female patients had significantly more abnormality of thyroid function more than male (P=0.03)

There was no difference regarding the symp-toms in the patient with normal or abnormal thyroid and adrenal gland (Table 6, 7).

Table 1 Clinical characteristics of 60 patients. thyroid and adrenal function

NO	SEX	AGE (Y)	RFI (mo.)	TD (GY)	TSH	FT4	FT3	ITT/ACTH	STAGE
1	F	31	84	76	↔	↓	↔	N	IV
2	F	24	33	70	↑	↓	↓	A	IV
2	F	42	51	70	↔	↓	↓	N	IV
4	F	40	47	66	↔	↓	↔	N	IV
5	M	32	108	70	↔	↔	↔	A	III
6	F	20	29	67	↔	↔	↔	A	IV
7	M	62	72	76	↑	↓	↔	N	IV
8	M	49	28	70	↔	↔	↔	N	IV
9	F	47	65	70	↓	↓	↓	N	IV
10	F	61	119	70	↑	↔	↓	N	IV
11	F	63	39	70	↔	↓	↔	N	IV
12	F	47	83	70	↓	↔	↔	N	IV
13	F	34	19	70	↔	↓	↓	N	IV
14	F	21	33	70	↔	↓	↓	N	IV
15	M	58	39	70	↔	↓	↓	N	IV
16	M	50	37	74	↔	↔	↔	N	IV
17	M	30	28	70	↔	↔	↔	N	IV
18	M	53	30	76	↔	↔	↔	M	IV
19	M	40	61	68	↑	↔	↔	M	IV
20	F	31	27	70	↑	↔	↔	M	IV
21	M	50	27	70	↔	↓	↓	A	IV
22	M	44	45	70	↔	↔	↔	A	IV
23	M	53	41	70	↔	↔	↓	N	IV
24	F	35	63	70	↔	↔	↔	N	IV
25	M	31	78	70	↔	↔	↔	N	IV
26	M	62	42	70	↔	↔	↓	N	IV
27	M	31	27	66	↓	↔	↔	N	IV
28	M	52	32	70	↑	↓	↑	N	IV
29	F	31	33	70	↔	↔	↔	N	IV
30	F	54	153	70	↔	↔	↔	N	I
31	M	51	120	71.4	↑	↔	↔	N	III
32	F	57	47	70	↑	↓	↔	N	IV
33	M	21	59	72	↔	↔	↓	N	IV
34	M	50	24	71.8	↔	↓	↔	N	IV
35	F	60	45	70	↑	↓	↔	N	III
36	M	62	47	70	↔	↓	↔	N	III
37	M	55	46	107	↑	↓	↔	N	IV
38	M	39	56	70	↔	↔	↔	N	IV
39	M	59	27	66	↔	↔	↔	N	III
40	M	55	24	70	↑	↓	↔	N	IV
41	M	19	30	70	↔	↓	↔	N	IV
42	F	30	22	74	↔	↓	↓	N	IV
43	M	48	120	72.5	↔	↔	↔	A	IV
44	M	55	47	70	↔	↓	↔	A	III
45	M	37	24	69	↑	↓	↔	N	IV
46	F	34	44	70	↔	↔	↔	N	IV
47	M	50	66	74	↑	↓	↓	A	IV
48	F	40	83	64	↔	↓	↔	N	IV
49	M	38	47	68	↔	↓	↓	N	IV
50	M	53	35	66	↔	↓	↔	N	IV
51	F	44	24	70	↔	↓	↓	N	IV
52	F	33	37	70	↑	↓	↓	N	IV
53	F	57	108	74.5	↑	↓	↓	N	IV
54	F	25	63	76	↔	↓	↓	A	IV
55	M	57	40	70	↔	↓	↓	N	IV
56	M	42	38	66	↔	↓	↓	N	III
57	M	60	47	70	↔	↓	↓	N	IV
58	M	41	80	65	↔	↓	↓	N	IV
59	M	54	95	70				N	III
60	M	49	192	66				N	IV
MEAN	44.2	55.2	70.7					N	I
SD	12.5	34.5	5.4						

RFI = Radiation free interval TD = Total dose ACTH = ACTH stimulation test

ITT = Insulin tolerance test N or ↔ = Normal, ↓ = Decrease, ↑ = increase, A = Abnormal.

F = Female M = Male

Table 2 Incidence of Hypothyroidism

Abnormal	Male	Female	Total (%)
Primary hypothyroid	5	6	11 (18.3)
Central hypothyroid	12	11	23 (38.3)
Subclinical hypothyroid	2	3	5 (8.3)

Table 3 Incidence of Adrenal insufficiency

Abnormal	Male	Female	Total (%)
Adrenal insufficiency	5	3	8 (13.3)

Table 4 Characteristics of the patients with abnormal thyroid function

	Abnormal	Normal	Significant
Male	19	17	Significant
Female	20	4	(P=0.03)
Mean age (year)	43.3±13.1	45.9±11.4	NS
Radiation free interval (month)	55.9±34.2	53.9±35.9	NS
Radiation dose (Gy)	70.9±6.5	70.3±2.4	NS

Table 5 Chracteristics of the patients with abnormal adrenal function

	Abnormal	Normal	Significant
Male	5	31	Significant
Female	3	21	(P=0.82)
Mean age (year)	42.0±14.5	44.6±12.3	NS
Radiation free interval (month)	67.3±39.2	53.3±33.8	NS
Radiation dose	71.0±2.5	70.7±5.8	NS

Table 6 Relationship of symptoms and adrenal gland function

Symptoms	Abnormal hormone (%)	Normal hormone (%)
Weakness	12.5	15.4
Fatique	12.5	19.2
Anorexia	12.5	7.7
Joint pain	12.5	3.9
Postural dizziness	37.5	9.6

Table 7 Relationships of symptoms and thyroid function

Symptoms	Abnormal hormone (%)	Normal hormone (%)
Decrease sweating	17.9	9.5
Cold intolerance	35.9	28.6
Decrease hearing	25.6	33.3
Hoarseness	20.5	4.8
Weight gain	12.8	4.8
Constipation	12.8	14.3
Muscle cramp	12.8	0
Paresthesia	7.7	4.8
Slow reflex relaxation	15.4	9.5

Discussion

After radiotherapy to the brain, abnormality of hypothalamic pituitary function has been reported [3-12]. Several reports also revealed symptomatic hypopituitarism in nasopharyngeal patients after receiving radiotherapy for 2-5 year[13,14].

Lam et al.[14] studied the function of pituitary gland and hypothalamus in 31 patients, the dose of radiation to pituitary gland and hypothalamus was 3,979±78 Gy and 6,167±100 cGy. After five years post radiotherapy, there were significant abnormal secretion of growth hormone 63.5%, gonadotropine 30.7%, corticotropine 26.7% and thyrothropine 14.9%.

Turner et al.[15] reported 32 patients with brain tumor who were followed for 2-13 years after received radiotherapy from 3,960 to 7,020 cGy. Most of the patients had abnormality of the function of pituitary and hypothalamus. The most frequent findings was gonadal dysfunction 61%, hypothyroid 28% and mild abnormality of the function of adrenal gland.

Our study in the nasopharyngeal cancer patients who were followed for at least two years and were without evidence of disease. There were evidence of abnormality in the secretion of thyroid glands (primary hypothyroid, secondary hypothyroid and subclinical hypothyroid) which was found in 65%, constituted primary hypothyroid 18.3%, central hypothyroid 38.3% and subclinical hypothyroid 8.3%. Abnormal of the function of adrenal glands was found in 13.3%.

Tunbridge et al.[16] reported the frequency of hypothyroid in general population of England, there were 1.9% incidence in female and 0.1% in male. Other report[17-21] found almost the same incidence with 2% in female an d 0.13% in male.

Our study revealed much higher incidence of hypothyroidism than normal incidence in general population. Hypothyroidism was found in 52.8% and 83.3% in male and female patients with nasopharyngeal cancer who received radiotherapy. Symptoms and signs are not predictor for hypothyroidism because there were no different in symptoms and signs for those patients with normal blood tests comparing to the groups with hypothyroidism.

Many reports revealed the incidence of 2.5-10.4% for subclinical hypothyroid[17-27]. Arem et al.[18]

reported the study from Japan in the study of the patients >40 years old, they found 3.2% incidence of subclinical hypothyroid for male and 5.5% for female. Our study found 8.3% of subclinical hypothyroidism, 40% in male and 60 % in female.

In this study, some of the patient also received chemotherapy, mainly cisplatin based during or after radiotherapy However, the effect of chemotherapy on thyroid glands has not been reported.[19-21]

The mechanism of abnormality of the function of the thyroid gland possibly due to follicle cells and vascular damages by radiation dose as low as 2.25 Gy[28]. The damage is not only involving the capillary but also fibrosis of thyroid capsule so the thyroid can not increase in size in order to meet the demand of the body resulting in hypothyroidism[29]. There is a report that radiation to the neck area may cause arteriosclerosis which in theory may effect the small arteries from the carotid especially superior thyroid artery[30]. There is also a report of increasing thyroid antibody after radiation to the neck[31]. In the patients who have mild thyroiditis, they may be more sensitive to thyroid antibody after radiation to the thyroid.

Central hypothyroid may occur from radiation given to the pituitary gland and/or hypothalamus. If the patients develops primary hypothyroid in which free T_4 is low and marked decrease in total T_4. The patient may develop central hypothyroid in which both free T_4 and total T_4 is low accompany with normal TSH, or slighter lower or higher TSH. All these patients should be treated with 25-200 µgram/day. But in the patient with severe hypothyroid should be treated with 100-150 µgram/day.

There are some controversy regarding treating the patient with subclinical hypothyroid who has high serum TSH but T_4 is normal. In general, we should start treating those patient with high TSH who also has abnormal symptoms or in the case of TSH over 10 µu/ml with increase antithyroid antibody because these patients may progress to develop overt hypothyroid.

There is no clear evidence that for patients who develop subclinical hypothyroid from radiation progress to overt hypothyroid. There is a report[17] revealed that the patients who receive radiation to the head and neck area developed 95% subclinical hypothyroid and 14.3% clinical hypothyroid. After 5-year follow up, clinical hypothyroid has increase to 40%. If this is the case, treatment for subclinical hypothyroid in this situation is reasonable as in the case of increase thyroid antibody.

There were some evidence that radiation in the animal to the thyroid developed increase TSH later on, may have increase risk of thyroid cancer. Patients with nasopharyngeal cancer who may live without disease for a long time may have a high risk of developing thyroid cancer so thyroid hormone may be necessary for these patients to bring down the TSH level in order to prevent thyroid cancer. So regular check up of the function of the thyroid may help identify the patient with subclinical disease.

It should be noted that the TSH in some patients with primary hypothyroid in this study was not as high as in the theory. Because in theory the relationship between the level of FT_4 and TSH is inverse proportion and it is log linear relation for example if the FT_4 level decrease 50%, the TSH increase 90 fold as 9,000% these patients may also have central hypothyroid in additional to primary hypothyroid.

Secondary adrenal insufficiency may also occur from radiation to pituitary gland or hypothala-

mus. In this study, adrenal insufficiency developed in 13.3%. The symptoms of adrenal insufficiency were not clearly shown in these patients.

In summary, because of the frequent development of the abnormality of the function of the thyroid and adrenal gland, the patients who receive radiation to the head and neck area should have endocrine assessment at 3 months post radiation and yearly thereafter.

References

1. Chiang Mai Cancer Registry. Annual Report 2006.
2. Khuhaprema T, Srivatanakul P, Sriplung H, Wiangnon S, Sumitsawan Y, Attasara P. Cancer in Thailand 1998-2000. Vol.IV. Bangkok Edical Publisher, 2007.
3. Bhandare N, Kennedy L, Morris G, Malyapa R, Mendenhall WM. Hypopituitarism after radiation therapy for extracranial head and neck cancers. Int J Radiat Oncol Biol Phys 2006;66(3):5187.
4. Blatt J, Lee P, Suttner J, Finegold D. Pulsatile growth hormone secretion in children with acute lymphoblastic leukemia after 1800 cGy cranial irradiation. Int J Radiat Oncol Biol Phys 1988;15:1001-6.
5. Constine LS, Woolf PD, Cann D. Hypothalamic-pituitary dysfunction after radiation for brain tumors. N Engl J Med 1993;328:87-94.
6. Fernandez A, Brada M, Zabuliene L, Karavitaki N, Wass J. Radiation-induced hypopituitarism. Endocrine-Related Cancer 2009;16(3):733-72.
7. Gleeson HK, Shalet SM. The impact of cancer therapy on the endocrine system is survivors of childhood brain tumours. Endocrine-Related Cancer 2004;11(4):589-602.
8. Littley MD, Shalet SM,Beardwell CG. Hypopituitarism following external radiotherapy for pituitary tumor in adults. Q J Med 1989;262:145-60.
9. Pomarede R, Czernichow P, Zucker JM. Incidence of anterior pituitary deficiency after radiotherapy at an early age: study in retinoblastoma. Acta Pediatr Scand 1984;73: 115-9.
10. Samaan NA, Schultz PN, Yand KP. Endocrine complications after radiotherapy for tumors of head and neck. J lab clin Med 1987;38:364-72.
11. Shalet SM, Beardwell CG, Morris-Jones PH, Pearson D. Pituitary function after treatment of intracranial tumor in children. Lancet 1975;2:104-7.
12. Yuen K, Cook D, Ong K, Chatelain P, Frykund L, Gluckman P, et al. The metabolic effects of short-term administration of physiological versus high doses of GH therapy in GH deficient adults. Clinical Endocrinology 2002;57:333-41.
13. Yoon SC, Suh TS, Jang HS, Chung SM, Kim YS, Ryu MR, et al. Clinical results of 24 pituitary macroadenomas with linac-based stereotactic radiotherapy. International Journal of Radiation Oncology, Biology, Physics 1998;41:849-53.
14. Lam KSL, Tse VK, Wang C. Effect of cranial irradiation on hypothalamic-pituitary function: 5-year longitudinal study in patients with nasopharyngeal carcinoma. Q J Med 1991:78:165-76.
15. Turner SL, Tiver KW. Thyroid dysfunction following radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 1995;31:279-90.
16. Tunbridge WMG, Evered DC, Hall R. The spectrum of thyroid disease in a community: The whickham survey. Clin Endocrinol 1977;7:481.
17. Helfand M, Bengtsson C, Lindquist O. Thyroid disease and high concentration of serum thyrotropin in a population sample of women. Acta Med Scand 1981;210:39-46.
18. Arem R, Escalante D. Subclinical hypothyroidism: epidemiology, diagnosis, and significance. Adv intern med 1996; 41:213-37.
19. Grande C. Hypothyroidism following radiotherapy for head and neck cancer: multivariate analysis of risk factors. Radiother Oncol 1992;25:31-6.
20. Posner MR, Ervin TJ, Fabian RL. Incidence of hypothyroidism following multimodality treatment for advanced squamous cell cancer of the head and neck. Laryngoscope 1984;94:451-4.
21. Ponsner MR, Weichselbaum RR, Fitzgerald JJ. Treatment complications after sequential combination chemotherapy and radiotherapy with or without surgery in previously untreated squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1985;11:1887-93.
22. Alterio D, Jereczek-Fosssa B,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(1):144-50.

23. Bhandare N, Kennedy L, Malyapa R, Morris CG, Mendenhall WM. Primary and central hypothyroidism after radiotherapy for head and neck tumor. Int. J Radiat Oncol Biol Phys 2007;68(4):1131-9.

24. Diaz R, Jaboin JJ, Morales-Paliza M, Koehler E, Phillips JG, Stinson S, et al. Hypothyroidism as a consequence of intensity-modulated radiotherapy with concurrent taxane-based chemotherapy for locally advanced head and neck cancer. Int J Radiat Oncol Biol Phys 2009;75: 1-9.

25. Tell R, Lundell G, Nilsson B, Sjodin H, Lewin F, Lewensohn R. Long-term incidence of hypothyroidism after radiotherapy in patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2004;60(2):395-400.

26. Wu YH, Wang HM, Chen HHW, Lin CY, Chen EYC, Fan KH, et al. Hypothyroidism after radiotherapy for nasopharyngeal cancer patients. Int J Radiat Oncol Biol Phys 2010;76(4):1133-9.

27. Sukthomya V, Sukthomya C. Thyroid dysfunction following external radiation for head and neck cancer. Thai J radio 1988;24:71-4.

28. Palmer BB, Gaggar N, Shaw HJ. Thyroid function after radiotherapy and laryngectomy for carcinoma of the larynx. Head and Neck Surg 1981;4:13-5.

29. Howes EL, Suoy JW, Harvey SC. The healing for wounds as determined by their tensite strength. JAMA 1929;92: 42-95.

30. Feehs RS, McQuirt WT, Bond MG. Irradiation: A significant factor for carotic artherosclerosis. Arch Otolaryngol Head and Neck Surg 1991;117:1135-7.

31. Markson JL, Flatman GE. Myxedema after deep x-ray therapy to the neck. South Med J 1965;1:1228-30.