The Effects of Neck Irradiation on Thyroid Gland for Tumors of the Head and Neck

—A prospective analysis of 75 cases—

In Kyu Park, M.D.[1], Sang Bo Kim, M.D.[1], Sang Mo Yun, M.D.[1]
Jun Sik Park, M.D.[2], Su Han Jun, M.D.[3] and Bo Wan Kim, M.D.[4]

Department of Radiation Oncology[1], Otolaryngology[2], General Surgery[3] and Internal Medicine[4], School of Medicine, Kyungpook National University, Taegu, Korea

=Abstract=

Seventy-five patients with tumors of the head and neck treated with either radiation therapy alone or combined with surgery or chemotherapy were studied prospectively to evaluate the effects of radiation therapy to the neck on thyroid gland between September 1986 and October 1992. All patients were serially monitored for thyroid function tests before and after radiation therapy. Radiation dose to the thyroid gland ranged from 35 to 60 Gy with a median dose of 50 Gy. Median follow-up time was 30 months with a range of 11 to 85 months.

The incidence of thyroid dysfunction was 40%: forty-five patients(60%) euthyroid, 2 patients(3%) clinical hypothyroidism, 27 patients(36%) subclinical hypothyroidism and 1 patient(1%) hyperthyroidism. No thyroid nodules or thyroid cancer were detected in any patients.

Thyroid dysfunction appeared earlier in patients who underwent surgery than in those patients treated with radiation therapy alone or combination of chemotherapy and radiation therapy($p=0.0013$). By multivariate analysis, risk factors that significantly influenced a higher incidence of thyroid dysfunction were female sex($p=0.0293$) and combination of total laryngectomy and radiation therapy($p=0.0045$).

In conclusion, evaluation of thyroid function before and after radiation therapy with periodic thyroid function tests are recommended to detect thyroid dysfunction in time and thyroid hormone replacement therapy is recommended whenever thyroid dysfunction develops.

Key Words : Head and neck tumor, Radiation therapy, Thyroid dysfunction

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INTRODUCTION

Thyroid dysfunction following radiation therapy to the neck during treatment of a variety of malignancies in the head and neck region was noted in the 1960s[1-3] and since then many studies on thyroid function after radiation therapy have been done in patients with tumors of the head and neck in whom the thyroid gland is unavoidably included in the radiation fields[2,4]. These studies have shown that clinical hypothyroidism is a unusual event with a incidence of 0 to 22%, but a high incidence of subclinical hypothyroidism has been reported to be 10 to 60%[1,5]. According to Maxon et al[6], the spontaneous incidence of hypothyroidism in general population has been estimated at 0.02% per year.

There are several reports of retrospective studies on the incidence of hypothyroidism after radiation therapy of a variety of malignancies in the head and neck, while prospective studies are rarely investigated[4,5,7].

To assess the effects of radiation to the neck on thyroid gland and to identify possible risk factors which might influence the appearance of radiation-induced thyroid dysfunction in tumors of the head and neck, a prospective study was initiated at the Department of Radiation Oncology, Kyungpook National University Hospital in 1986.

MATERIALS AND METHODS

The study consisted of previously untreated patients with tumors of the head and neck who were treated at the Department of Radiation Oncology, Kyungpook National University Hospital between September 1986 and October 1992. This study included all patients receiving radiation therapy to the head and neck area in whom the entire thyroid gland was included within the radiation fields. Patients excluded from this study were those 1) with a prior history of thyroid disease, 2) with prior thyroid surgery, 3) with abnormal thyroid function before radiation therapy, 4) with tumor invasion to thyroid gland, 5) unable to complete whole course of radiation therapy and 7) lost to follow-up. Seventy-five patients were included in this study and were followed prospectively for 11 months and 85 months, with a median of 30 months. The clinical characteristics of the patient population are summarized in Table 1. Patient age ranged from 17 to 73 years with a median age of 52 years. There were 54 men and 21 women, a sex ratio of 2.6:1. Treatment was radiation therapy alone in 9 patients, surgery and postoperative radiation therapy in 28 patients and radiation therapy combined with chemotherapy in 38 patients. The distribution of the patients by histological diagnosis is shown in Table 2.

Table 1. Patients Characteristics

Characteristics	
No. of Patients	75
Age(in year)	
Median	52
Range	17–73
Sex	
Female	21
Male	54
Treatment Group	
RT alone	9
CTX+RT	38
Surgery+RT	28
Follow-up(Month)	
Median	30
Range	11–85

Radiation therapy was delivered with a 6MV linear accelerator. The upper neck area was treated through bilaterally opposed lateral fields with appropriate spinal cord shielding. The lower necks and supraclavicular areas were treated with single anterior field. In general, gross disease received 60 to 75Gy. Postoperative patients received 50 to 60Gy and uninvolved lymph node groups received 45 to 50Gy. In patients with Hodgkin's disease, mantle irradiation was applied. This technique included shielding

Table 2. Patients Distribution by Histological Diagnosis

Diagnosis	No. of patients
Hodgkin's Disease	2
Non-Hodgkin's Disease	15
Head and Neck Carcinoma	58
Oral Cavity	4
Oropharynx	6
Nasopharynx	17
Hypopharynx	5
Larynx	18
Paranasal Sinus	1
Salivary Gland	2
Unknown Primary of Neck	5
Total	75

the larynx anteriorly and the cervical cord posteriorly. The radiation dose of the thyroid is estimated to be identical to the tumor dose of radiation delivered to the neck and radiation dose to the thyroid gland ranged from 35 to 60Gy with a median dose of 50Gy. Surgery consisted of either total laryngectomy with neck dissection or neck dissection alone. Total laryngectomy with neck dissection was carried out in 21 patients and neck dissection alone in 7 patients. Chemotherapy consisted of either two cycles of CVB (cyclophosphamide, vincristine and bleomycin) or CF(cisplantin and 5-FU) for head and neck cancers, 6 cycles of MOPP(nitrogen mustard, vincristine,procarbazine and prednisone) for Hodgkin's disease and 6 cycles of CHOP-BLEO (cyclophosphamide ,adriamycin,vincristine, prednisone and bleomycin) for non-Hodgkin's lymphoma.

All patients had a clinical assessment and measurement of thyroid function by radioimmunoassay before and after radiation therapy. The in-vitro thyroid function tests included measurement of serum total T3, total T4, free T4 and TSH levels. Serum TSH level was measured before and after administration of TRH in cases with elevated serum TSH levels. TRH(0.4mg) was administered as a single intravenous bolus and blood was collected for measurement of TSH levels before and at 15, 30 and 60 minutes after administration. Additionally, the serum levels of antimicrosomal and antithyroglobulin antibody titers were measured in order to exclude autoimmune disease. Thyroid function tests were determined at approximately 6 to 12 months and upto 6 times after radiation therapy. The thyroid function was classified as follows: Euthyroidism(normal thyroid hormonal levels and no clinical symptoms of hypothyroidism), subclinical hypothyroidism(increased basal TSH, increased TSH response to TRH, normal T3-T4 levels and no clinical symptoms of hypothyroidism) and clinical hypothyroidism(increased basal TSH,increased TSH response to TRH,decreased T3-T4 levels and clinical symptoms of hypothyroidism).

In order to evaluate the risk factors which influence the appearance of radiation-induced thyroid dysfunction, a multivariate analysis using Cox's regression proportional hazards model carried out.

RESULTS

Seventy-five patients were followed with serial evaluation of thyroid function. Upto August 1993, the incidence of thyroid dysfunction following radiation therapy for tumors of the head and neck was 40.0%(Table 3). Twenty-seven patients(36%) had subclinical hypothyroidisdism and 2 patients(3%) had clinical hypothyroidism. Only 1 case(1%) of hyperthyroidism was observed.

The distribution of thyroid hormone levels for the different groups of patients in relation to thyroid function before and after radiation therapy is presented in Table 4. As shown in Table 5, patients who underwent surgery developed thyroid dysfunction more earlier than patients receiving radiation therapy alone or radiation therapy and chemotherapy($p=0.0013$). Multivariate analysis was used to find out possible factors that influence high incidence of thyroid dysfunc-

Table 3. Incidence of Thyroid Dysfunction following Radiation Therapy

	No. of Patients
Hypothyroidism	29(39%)
Subclinical	27(36%)
Clinical	2(3%)
Hyperthyroidism	1(1%)
Euthyroidism	45(60%)
Total	75(100%)

Table 4. Distribution of Thyroid Hormone Levels in relation to Post-irradiation Thyroid Function (Median)

	TSH(ug/ml)		T3(ng/ml)	
Thyroid Function	PreRT	PostRT	PreRT	PostRT
Euthyroid	1.1	2.0	1.4	1.4
Hypothyroidism	1.4	25.7	1.3	1.3
Hyperthyroidism	0.4	0.1	1.3	2.1

	T4(ug/dl)		FT4(ng/dl)	
Thyroid Function	PreRT	PostRT	PreRT	PostRT
Euthyroid	9.1	8.9	1.3	1.2
Hypothyroidism	8.4	7.4	1.1	1.0
Hyperthyroidism	10.7	13.3	1.6	2.2

Table 5. Time to Appearance of Thyroid Dysfunction after Radiation Therapy

Treatment Group	No. of Patients	Time to Thyroid Dysfunction (median in month)	
RT alone	1 (1/9)	11	
CTX+RT	14(14/38)	46	0=0.0013
Surgery+RT	15(15/28)	16	

tion(Table 6). Significant risk factors associated with a higher incidence of radiation-induced thyroid dysfunction were female sex($p=0.0293$) and combination of laryngectomy and radiation therapy(0.0045). Table 7 and 8 show the distribution of patients according to thyroid dysfunction and significant factors of the multivariate analysis. Female sex was associated with an incidence of thyroid dysfunction of 57% compared with 33% in male(Table7). Twelve of the 21 female patients developed thyroid dysfunction while eighteen of 54 male patients developed thyroid dysfunction.

Table 6. Risk Factors Influencing the Incidence of Thyroid Dysfunction after Radiation Therapy: Multivariate Analysis

Factor	Regression coefficient	Relative risk	Standard error	P-value
Age	-0.0243	0.976	0.0189	0.1981
Sex	-1.0260	0.358	0.4707	0.0293
CTX	1.5263	4.601	1.1646	0.1900
RT Dose	-0.0003	1.000	0.0006	0.6029
Combination of neck dissection only	1.4747	4.370	1.2634	0.2431
Combination of total laryngectomy	3.4035	30.069	1.1991	0.0045

Table 7. Effect of Sex on Thyroid Dysfunction after Radiation Therapy

Thyroid function	Female	Male	Total
Euthyroidism	9(43%)	36(67%)	45
Hypothyroidism	11(52%)	18(33%)	29
Hyperthyroidism	1(5%)	0(0%)	1
Total	21	54	75

Table 8. Effect of Surgery on Hypothy-roidism after Radiation Therapy

Surgical Procedure	No. of patients	Hypothy-roidism	Euthy-roidism
Neck dissection only	7	1(14%)	6(86%)
Laryngectomy+ neck dissection	21	14(67%)	7(33%)

The effect of surgery on the development ofthyroid dysfunction is shown in Table 8. Thyroid dysfunction developed in fewer patients undergoing neck dissection only as compared with patients receiving a laryngectomy with neck dissection. Only 1(14%) of 7 patients with neck

dissection alone developed thyroid dysfunction while 14(67%) of 21 patients with laryngectomy and neck dissection developed thyroid dysfunction.

Age, radiation dose to thyroid gland, combination of chemotherapy and radiation therapy, and combination of radiation therapy and surgery with neck dissection only did not significantly influence the incidence of thyroid dysfunction by multivariate analysis. We observed thyroid dysfunction in 33.3%(4/12) of patients receiving < 50 Gy and in 41.2%(26/63) of those treated at 50 Gy($p=0.6029$).

In this study, 60% of patients was classified as euthyroid during the follow-up.

DISCUSSION

Currently, radiation therapy, either alone or in combination with surgery or chemotherapy, has an important role in the therapy for tumors of the head and neck. External radiation therapy portals usually include the thyroid gland within the fields of radiation. Although the normal thyroid gland is transitionally considered to be resistant to external radiation, thyroid dysfunction is a common complication following radiation therapy for tumor of the head and neck with a incidence of 10 to 60 %[2,4,5,8,9]. This widely differing incidences of thyroid dysfunction after radiation therapy may be due to a combination of years of follow-up, the sensitivity of the thyroid function tests and whether surgery was a part of the treatment procedure[2,3,5].

In this study, the incidence of the thyroid dysfunction was 40%. Two patients(3%) with clinical hypothyroidism were observed while 36% showed subclinical hypothyroidism. Only one case(1%) of hyperthyroidism was observed. Several studies have reported the issue of thyroid dysfunction in patients with lymphoma and cancer of head and neck. Posner et al[7] found a 25% of incidence of hypothyroidism in patients with radiation therapy only and a 45% of incidence in patients with receiving neck surgery and radiation therapy.

Feyerabend et al[5] reported an incidence of hypothyroidism of 29% after radiation therapy to head and neck. Shafer et al[9] found an incidence of clinical hypothyroidism in 20% and subclinical hypothyroidism in an additional 12% of patients. Fuks et al[4] reported an incidence of subclinical hypothyroidism of 38% following radiation therapy to the head and neck. Twenty percent of patients with radiation therapy only and 62% of surgery and radiation therapy in Shafer's series had hypothyroidism[9]. Overall these results do not differ from our studies.

In contrast to hypothyroidism, only one case of clinical hyperthyroidism was found in this study. Although the number of patients was small, there were case reports with hyperthyroidism associated with external radiation to the head and neck for malignant diseases[10]. Close relationship of Hashimoto's thyroiditis and Grave's disease and their autoimmune nature have been well known and irradiation to the thyroid and other systems may play an important role in the development of organ specific autoimmune disease of the thyroid[10,11].

We have confirmed the predisposition of female sex to develop thyriod dysfunction. Posner et al[7], Vrabec et al[8] and Grande[2] reported that female sex had a higher incidence of thyroid dysfunction after radiation therapy for head and neck cancer, while others reported no sex difference in patients treated for tumors of the head and neck[3,11-13]. The reason for the increased incidence of thyroid function in the female sex can not be readily explained. It might be speculated that the female thyroid gland is more sensitive to the adverse effects of radiation therapy or that overall female thyroid reserve is decreased and the incidence of hypothyroidism spontaneously occurring in female is greater than 10 times that observed in male[7,14]. Another possible explanation is that hypothyroidism may be somehow related to estrogen levels[8].

We have shown that surgery and radiation therapy, specially when a laryngectomy is per-

formed, leads to increased the risk of thyroid dysfunction, as has also seen in many studies[2,4,7,9,15,16]. It has been postulated that the removal of a part of thyroid gland or the damage of the thyroid arterial supply during the surgery could facilitate the development of hypothyroidism after radiation therapy. It has also speculated that irradiation, while little or no effect when given alone, prevents the normal compensatory hypertrophy after thyroidectomy and thereby contributes to the high incidence of hypothyroidism[9]. Whatever mechanism, these results show that there is a considerable risk of patients developing hypothyroidism after laryngectomy and radiation therapy.

In patients who underwent surgery, hypothyroidism appeared earlier than in those treated with chemotherapy and radiation therapy or radiation therapy alone. This result is similar to Posner's series[7].

Subclinical hypothyroidism can be converted to overt clinical evidence of hypothyroidism unless subclinical hypothyroidism are treated by thyroid hormonal replacement[7]. In this study, we observed that 2 of 3 patients with subclinical hypothyroidism who were not treated by hormonal replacement progressed to clinical hypothyroidism. Therefore, it is reasonable to initiate thyroid hormonal replacement when subclinical hypothyroidism develops. Maxon et al[6] found that the majority of thyroid nodules or thyroid cancer reported following external irradiation had occurred after doses not exceeding 20Gy. A dosage of 30Gy or more would be likely to sterilize the thyroid follicular cells and render the thyroid gland atrophic rather than neoplastic[17,18]. In the present study, no case of new thyroid nodules or thyroid cancer could be detected, which may be due to the short follow-up and doses exceeding 20Gy. However, only a handful cases of thyroid carcinoma has been reported after radiation doses exceeding 20Gy in the literatures[19,21]. This can be regarded to result from irradiation initiated carcinogenesis promoted by the TSH-induced hyperplasia of surviving non-sterilized follicular cells[10,17]. It would be appear reasonable to monitor thyroid function and administer thyroid hormone supplement when subclinical or clinical hypothyroidism develops, thus removing the promoting carcinogenic action of TSH stimulation.

CONCLUSIONS

Seventy-five patients with tumors of the head and neck were studied prospectively in order to evaluate the effects of radiation therapy on thyroid gland. The following conclusions were reached.

1) Thyroid dysfunction is a common complication of the radiation therapy for the tumor of head and neck.

2) Risk factors that significantly influence a higher incidence of thyroid dysfunction were female sex and combination of laryngectomy and radiation therapy.

3) Thyroid dysfunction appeared earlier in patients who underwent surgery than in those patients treated with radiation therapy alone or combination of chemotherapy and radiation therapy.

4) In those patients with thyroid gland within the fields of radiation, evaluation of the thyroid function before radiation therapy as well as periodic thyroid function studies after radiation therapy, especially when a laryngectomy is performed, are recommended.

5) Thyroid hormone replacement therapy is recommended whenever thyroid dysfunction develops.

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=국문초록=

두경부종양 환자에서 경부 방사선조사가 갑상선기능에 미치는 영향
— 75예의 전향적 분석 —

경북대학교 의과대학 치료방사선과학교실[1]
이비인후과학교실[2], 외과학교실[3], 내과학교실[4]

박인규[1] · 김상보[1] · 윤상모[1] · 박준식[2] · 전수한[3] · 김보완[4]

1986년 9월부터 1992년 10월까지 경북대학교병원 치료방사선과에서 방사선치료 단독요법이나 수술 혹은 화학요법과의 병합요법으로 치료받은 두경부종양 환자 75명을 대상으로 경부 방사선조사가 갑상선기능에 미치는 영향을 평가하기 위하여 전향적 조사를 실시하였다.

모든환자는 방사선치료전 및 방사선치료후에 정기적으로 임상검사 및 갑상선 기능검사를 시행하였다. 갑상선조사선량은 35Gy에서 60Gy였고 그 중앙값은 50Gy였으며 추적관찰기간은 11개월에서 85개월로 중앙추적기간은 30개월 이었다.

결과를 보면 갑상선 기능이상의 빈도는 40%(30명)이었다. 45명(60%)은 갑상선 기능이 정상 이었으며 2명(3%)은 임상적 갑상선 기능저하증 이었고 27명(36%)은 준임상적 갑상선 기능저하증 이었다. 갑상선 기능항진증이 1명(1%)에서 발견되었으며 갑상선 결절이나 악성종양은 발견되지 않았다.

수술 및 방사선치료군에서 갑상선 기능이상이 다른 치료군에서보다 일찍 발생하였다($p=0.0013$). 다변량분석에 따르면 방사선치료후 갑상선 기능이상의 발생빈도에 영향을 주는 위험인자는 여성($p=0.0293$) 및 전후두절제술과 방사선치료의 병합요법($p=0.0045$)였다.

결론적으로 방사선치료후 정확한 시기에 갑상선 기능이상을 발견하기 위하여 방사선 치료전 및 방사선치료후에 정기적인 갑상선 기능검사가 필요하며 갑상선 기능이상이 발견되면 즉시 갑상선 호르몬제재 치료를 하여야 하겠다.