Original Article

Radiation-induced Hypothyroidism in Head and Neck Malignancy

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ABSTRACT

Background and Objective: Hypothyroidism is a known consequence of the external beam radiotherapy to the neck encompassing the thyroid gland for over 40 years. The aim of this study was to find out the incidence of hypothyroidism in patients with head and neck cancer treated with radiotherapy, when radiation portals included whole of the thyroid gland.

Materials and Methods: This prospective non-randomized study was conducted from December 2004 to February 2006. In this regard, 39 patients with head and neck malignancies referred to radiation oncology center of Hamedan whom treated with the external beam radiotherapy, whose radiation portals included the whole of the thyroid gland. Thyroid function tests were done at the beginning of treatment, one month, three months, six months, and one year after the completion of radiotherapy.

Results: Out of 39 patients, two were excluded from the study as they had history of hypothyroid before the initiation of treatment. The next two were excluded from data analysis because they did not undergo regular follow-up. Of the patients attending the follow-up clinic, 31% were found to have sub-clinical hypothyroidism (TSH>4.5 mU/l) during a year.

Conclusion: Since a significant number of patients developed hypothyroidism following radiotherapy on the neck, thyroid function tests should be included in the routine follow-up protocol of such patients. Certain questions have emerged from this study, which need a large randomized study to find out the answers.

Key words: Hypothyroidism, Thyroid function tests, Cancer of Head and neck

Introduction

Carcinoma of the head and neck region is the 5th most common malignancy worldwide (1), probably due to increased usage of alcohol and smoking. External beam radiation is an integral part of management of such malignancies, used either alone (in early-stage tumors) or in combination with surgery and/or chemotherapy (in advanced stages). Target volume of irradiation usually includes whole of the thyroid gland.

Thyroid gland is one of the major human's endocrine glands with the average weight of 12-20 grams (2). Its function is production and storage of thyroid hormones under control of hypophysis and hypothalamus by TSH and TRH respectively. For secretion control, T3 and T4 have negative feedback on secretion of TSH from pituitary gland (3). Primary hypothyroidism can be created due to autoimmune disease (Hashimoto's thyroiditis), surgical resection, iodine therapy, and

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radiotherapy (4). However, adult thyroid cells are relatively radio-resistant due to their low proliferative index (5). Hypo-function of the thyroid gland is a known side effect of external radiotherapy to the head and neck malignancies (6) more than 40 years ago (7). Early manifestation of sub-clinical primary radiation-induced hypothyroidism is increasing of TSH (2, 8-10). After external beam radiotherapy to the neck, the documented incidence of sub-clinical hypothyroidism varies widely up to 14% after six months, 27% after 12 months, 45% after 24 months (11), and more than 50% (2, 6, 12-13) on long time follow-up with radiation dose greater than 25-30 Gray (6, 14). In other studies, radiation-induced hypothyroidism has been more common in children and in small age patients (15) and in senile ones (16). Addition of surgery to the neck region vastly increases the incidence of hypothyroidism, but addition of chemotherapy probably has little or no effect (17). Though hypothyroidism has a significant impact on the quality of life, assessment of thyroid function should be included as a part of routine follow-up of head and neck cancer patients prior to expression of frank clinical hypothyroidism, especially in children and senile cases due to their greater morbidity.

Therefore, in this study we have tried to assess risk of developing hypothyroidism in our patients with head and neck malignancies, where radiation portals included the whole of the thyroid gland.

Materials and Methods

This prospective nonrandomized study was conducted from December 2004 to February 2006. In this respect, 39 patients were included which their histopathology proved head and neck malignancy and were destined to receive external beam radiotherapy to the primary site as well as to the neck, and whose radiation target volume will include whole of the thyroid gland at Department of Radiation Oncology of Hamedan. Patients having thyroid metastases, a positive history of thyroid diseases, or thyroid surgery were excluded from this study. Before the initiation of radiotherapy all patients underwent detailed history taking and physical examination, including thyroid gland, complete blood count (CBC), and measurement of TSH. Eligible patients treated with linear accelerator (linac) 6 MV using treatment planning and radiotherapy to the primary site as well as to the neck covering the entire of the thyroid gland and all thyroid function tests performed at the same laboratory. Proposed dose of radiotherapy was 4000-6600 cGy in 23 to 33 fractions over a period of 32 to 45 days and was delivered by parallel opposing beams. Those patients who had TSH serum level higher than 4.5 mU/l were considered as sub-clinical hypothyroid state. Detailed history and physical examinations with particular emphasis on those of hypothyroidism were done in every follow-up visit and thyroid function tests were repeated at one month, three months, six months, and one year after completion of radiation. We estimated the risk of hypothyroidism in this study using Chi-Square and Fisher`s Exact tests and SPSS software (version 15).

Results

Out of the 39 patients studied, four were excluded, two of them had a positive history of sub-clinical hypothyroidism and consumption of thyroid hormone (levothyroxin) and two others omitted due to irregular follow-up. Meanwhile, 35 patients were available for the study with a mean age of 43.2 years, of whom 18 patients were male with a mean age of 49.3 years and 17 were female with a mean age of 36.2 years whom received radiotherapy. Patients' histopathological characteristics are shown in Table 1.

Table 1. Histopathology and frequency of primary tumor site

Location	Number	Frequency
Larynx	8	23%
Hypopharynx	6	17%
Nasopharynx	7	20%
Oral cavity	5	14%
Lymphoma (supra diaphragmatic early stage)	6	17%
Others (salivary gland, etc)	3	9%
Total	35	100%

All of the patients received external beam radiotherapy. In this regard, 11 patients received 4000 cGy and 24 patients received 6000-6600 cGy. Thyroid glands received radiation doses between 4120 and 6250 cGy according to DVH (dose-volume histogram). All of the selected patients were euthyroid at the beginning of therapy but the incidence of hypothyroidism increased with time. The results have been shown in Table 2.

Table 2. Frequency of hypothyroidism after head and neck radiotherapy

Post-radiation time period	Total number	Frequency	Male = 8 cases		Female = 10 cases	
			Number	Frequency	Number	Frequency
After 1 month	0	0	0	0	0	0
After 3 months	0	0	0	0	0	0
After 6 months	7	20%	3	17%	4	23.5%
After 12 months	11	31%	5	28%	6	35%

The time period was calculated from the date of completion of radiotherapy. According to the results of our study, all patients were euthyroid after one and three months of completing radiotherapy, but after six months 20% (23.5% for females and 17% for males) and after one year 31% (35% for females and 28% for males) of cases with a mean age of 34.5 years (24.5 for females and 46 for males) were sub-clinical hypothyroid (Table 3) (p=0.028).

Table 3. Frequency distribution of hypothyroidism according to the age one year after termination of radiotherapy

Age groups	Total number of cases	Number of hypothyroidism	Frequency
1-20 Years	5	3	60%
21-40 Years	12	3	25%
41-60 Years	11	2	17%
61-80 Years	7	3	43%
1-80 Years	35	11	31%

Discussion

Besides surgical intervention, radiotherapy is one of the known curative management for the patients with head and neck malignancies. It may be used either alone or in combination with surgery and/or chemotherapy. In 1961, Felix et al (7) first reported a case of hypothyroidism six years after treatment with external radiotherapy in a case of laryngeal carcinoma. Since then, several other investigators have reported the occurrence of hypothyroidism in patients who received radiotherapy in the neck region. Despite these reports, tests for thyroid functions are not yet included routinely in the follow-up protocols of patients with head and neck malignancies at all centers (18). Estimation of the magnitude of the problem is very difficult and confusing because of the fact that some series have included patients treated with radiotherapy alone (19), while others have included patients that had hemi-thyroidectomy as a part of laryngectomy, in addition to pre-or post-operative radiotherapy (20) and others have included patients with radiotherapy and chemotherapy concurrently or as sequential. In their study, Mercado et al (21) reported 48% and 67% projected incidence of hypothyroidism at 5 and 8 years respectively, when patients with head and neck malignancies were treated with external beam radiotherapy with or without concurrent chemotherapy. The median time to development of hypothyroidism was 1.4 years, Turner et al (22) reported incidence of 23.8% sub-clinical hypothyroidism following radiotherapy to the whole of the thyroid gland. They estimated that by 5 years, up to 40% of the patients might become hypothyroid. Tell et al (23) reported a lower incidence. They treated 264 patients with head and neck malignancies by external beam radiotherapy and at a median follow-up of 19 months, 22% developed sub-clinical hypothyroidism. Median time to develop hypothyroidism was 15 months. In their series, incidence of sub-clinical hypothyroidism was significantly higher when whole of the thyroid gland was included in the target volume compared to patients where only part of the thyroid gland was irradiated. There is a general agreement that hypothyroidism is a much more common complication following radio-therapeutic management of head and neck cancers with a frequency ranging from 43 to 66% (9, 11, 13, 17, 24-25) and sometimes up to 80% (26) and more (27), often depending upon the duration of follow-up.

In this study after one year, overall incidence of sub-clinical hypothyroidism of our reported patients was 31%. Despite the diversity of reported incidences, type of managements and duration of follow-up in published series, our results are comparable with others. Since radiation-induced hypothyroidism is a late effect, it is expected that with the passage of time, the incidence will increase and some of the patients with sub-clinical hypothyroidism will progress to clinical hypothyroidism. Dose of radiation required to produce

hypothyroidism is also confusing. DeGroot (28) and Hancock et al (29) suggested that radiation doses in the range of 3000 to 8000 rads are required to produce hypothyroidism. At the same time, Hancock et al (29) reviewed 1787 patients of Hodgkin's disease treated with Mantle field irradiation at the dose of 3500-4500 cGy and estimated a 43% actuarial risk of developing hypothyroidism at later years. Doses greater than 2500-3000 cGy with mantle technique have produced hypothyroidism in more than 50% of cases at long time follow-up (6, 14). How radiotherapy produces hypothyroidism is also incompletely understood. This may be due to direct follicular destruction or prevention of cell division or vascular damage to the thyroid gland or immunologically mediated damage to the thyroid gland or a various combination of the mentioned factors. Histological examination of the thyroid gland after external irradiation has documented follicular cell damage and vascular damage following doses as low as 225 cGy (19). An immunologic influence has been suggested by Einhorn and Wikholm (22). Because adult thyroid cells in vivo are not expected to have a high turnover rate and are well-differentiated, it has been postulated that they may undergo radiation-induced apoptosis, varying between different patients. We found no effect of primary site, neck node status, or stage of disease on the incidence of hypothyroidism. A similar result was findings of Mercado (21) and Tell (11, 13, 15, 23). According to the results of our study, patients on both extremes of age are more prone for radiation-induced hypothyroidism as other studies (11, 14) but mean age of our patients were lower than other studies, i.e. 34.5 versus 41 years, with predominance of female to male (35% versus 23%), probably due to high incidence of cancer at young age group in our country and more prevalence of endemic hypothyroidism, especially in females.

Conclusion

According to the results of our study, 31% of patients were found to have sub-clinical hypothyroidism after one year. Because supplementation of thyroxin will vastly change the quality of life of the hypothyroid patients, it seems to be mandatory. But after one year of study, there are some questions that must be answered by conducting large randomized studies preferably multi-centered to answer these questions: 1. when should we to start the thyroid function test, 2. how long it will be carried out in euthyroid patients, 3. how often the test should be done. Finally, one thing can be said with certainty that thyroid function tests should be included in the follow-up protocol of patients receiving radiation to the neck encompassing thyroid gland.

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