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Original Article / Çalışma - Araştırma

Post-radiotherapy hypothyroidism in head and neck cancers: When should we be concerned?

Baş-boyun kanserlerinde radyoterapi sonrası hipotiroidi: Ne zaman endişelenmeliyiz?

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ABSTRACT

Objectives: This study aims to analyze the incidence of hypothyroidism (HT) in patients who underwent radiotherapy (RT) for head and neck cancers (HNC), and to determine risk factors.

Patients and Methods: This study was a retrospective analysis of patients who were treated with RT alone or in combination with surgery and/or chemotherapy between January 2005 and May 2012. Patients were grouped according to the primary tumor site, TNM staging system, age, gender, total radiation dose (TRD), mean radiation dose of thyroid gland (MRT), neck dissection, and chemotherapy.

Results: A total of 90 patients who were treated with RT were analyzed. The median age was 52±13 (range, 12-87) years. The histopathologic finding of 88 patients was squamous cell carcinoma, others were adenocystic carcinoma and undifferentiated carcinoma. The median follow-up of all patients after RT was 15 (range, 6-72) months. Post-radiotherapy HT was found in 31 patients (34.4%). In this group, clinical and subclinical HT was present in eight (26%) and 23 (74%) patients, respectively. Age younger than 60 years and increased MRT (especially mean thyroid dose 20 Gy<) were significant risk factors for post-radiotherapy HT ($p<0.05$).

Conclusion: Physicians should pay more attention to HT in patients who were treated with RT for HNC during follow-up.

Keywords: Head and neck cancers; hypothyroidism; mean radiation dose of thyroid gland; radiotherapy; thyroid gland.

ÖZ

Amaç: Bu çalışmada, baş-boyun kanserlerinde (HNC) radyoterapi (RT) uygulanan hastalarda hipotiroidi (HT) insidansının analiz edilmesi ve risk faktörlerinin belirlenmesi amaçlandı.

Hastalar ve Yöntemler: Bu çalışma, Ocak 2005 - Mayıs 2012 tarihleri arasında tek başına RT ile tedavi edilen veya cerrahi veya kemoterapi ile kombine edilen hastaların retrospektif bir analizidir. Hastalar primer tümör, TNM evreleme sistemi, yaş, cinsiyet, total radyasyon dozu (TRD), tiroid bezinin ortalama radyasyon dozu (MRT), boyun diseksiyonu uygulaması ve kemoterapiye göre gruplandırıldı.

Bulgular: Radyoterapi ile tedavi edilen toplam 90 hasta analiz edildi. Medyan yaş 52±13 (dağılım, 12-87) yıl idi. Seksen sekiz hastanın histopatolojik bulgusu skuamöz hücreli karsinom, diğerleri adenokistik karsinom ve indifferansiye karsinom idi. Radyoterapi sonrası tüm hastaların medyan takip süresi 15 (dağılım 6-72) ay idi. Post-radyoterapi HT, 31 hastada (%34.4) bulundu. Bu grupta sırasıyla sekiz (%26) ve 23 (%74) hastada klinik ve subklinik HT vardı. Altmış yaşın altındaki yaş ve MRT artışı (özellikle ortalama tiroid dozu 20 Gy<), radyoterapi sonrası HT için anlamlı risk faktörleri idi ($p<0.05$).

Sonuç: Hekimler, takip sırasında HNC için RT ile tedavi edilen hastalarda HT'ye daha fazla dikkat etmelidirler.

Anahtar Sözcükler: Baş ve boyun kanserleri; hipotiroidizm; tiroid bezinin ortalama radyasyon dozu; radyoterapi; tiroid bezi.

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The treatment of head and neck cancers (HNC) has a multi-modality concept and multi-disciplinary approach with experienced physicians including a head and neck surgeons, radiation oncologists, and medical oncologists. An appropriate approach for early-stage cancers (T_1 and some T_2) with no nodal involvement is surgery or radiotherapy, depending on the location of the tumor and experience of physicians. Surgery and radiotherapy (RT) combined can be effective in intermediate-stage tumors, such as infiltrative tumors and some T_2 or exophytic T_3 tumors, with N_0 or N_1 neck disease. The best concept for the treatment of locally-advanced tumors (stage T_3 or T_4 with N_2 or N_3 neck disease) is concurrent chemoradiotherapy (CRT).[1]

Hypothyroidism (HT) is a systemic medical condition that comprises fatigue, wound healing deceleration, cold intolerance, hair loss, constipation, weight gain, dry skin, and hoarseness. Routine assessment of thyroid function in follow-up is not commonly undertaken in patients receiving RT for HNC, which may result in failure to detect and treat a reversible cause of morbidity for a significant proportion of surviving patients.[2]

Hypothyroidism after RT alone or in combination with surgery and/or chemotherapy for HNCs has been well reported between 17% and 51% in the literature.[3-6] However, thyroid dysfunction after RT for HNC still represents a clinically underestimated problem.[7]

Our study is based on the question of "When should we be concerned for post-RT HT?" with assessment of multiple variables in patients treated with RT for HNCs. At the end of the study, we think that physicians will find the answer to this question and be more aware of HT in these patient groups.

PATIENTS AND METHODS

Subjects

This study was a retrospective analysis of patients who were treated with RT alone or in combination with surgery and/or chemotherapy between January 2005 and May 2012. Patients with thyroid gland disease or abnormal thyroid hormone levels or who underwent thyroid gland surgery were excluded from this analysis. In addition, patients with HNCs (e.g., nasopharynx, mid-facial or paranasal tumors), in whom radiation affects the pituitary gland resulting in central HT, were excluded from the study.

Patients were grouped according to the tumor, node, metastasis (TNM) staging system of the American Joint Commission on Cancer (AJCC), the primary tumor site, age, sex, total radiation dose (TRD), mean radiation dose of thyroid gland (MRT), neck dissection and chemotherapy.

Treatment details

Three-dimensional conformal RT or intensity-modulated radiotherapy (IMRT) was performed for each patient using a thermoplastic mask. Each patient underwent routine computed tomography (CT) of the head and neck region. The CT data were transferred to the RT treatment planning system. All patients were irradiated with once-daily fractionation at 1.8-2.0 Gy/d with 6-MV photon beams for five days a week. The primary tumor site was treated with irradiation of 60 to 66 Gy and the lymphatic site received a total radiation dose of 50 to 54 Gy for early-stage selected cancers (i.e. nasopharynx carcinoma). For intermediate-stage tumors, primary and nodal metastasis sites (T_2-T_3 staging and N1 nodal disease) were treated with primary or postoperative adjuvant irradiation dose 70 Gy and adjacent nodal sites were irradiated with 54 to 57 Gy. After the induction therapy with cisplatin (75 mg/m^2) and taxotere (75 mg/m^2) for three days, concomitant CRT (cisplatin 100 mg/m^2 was given twice concurrent with IMRT for once per week for three weeks was used for more advanced tumors.

Surgical treatment of the primary tumor site was performed with adequate resection in selected tumors. Neck dissection was made as a radical, modified or selective neck dissection according to the staging.

The thyroid gland was contoured manually on the CT scans and the absorbed doses were calculated on individually-produced dose plans (Figure 1). Additionally, mean radiation doses of thyroid glands were grouped with 0-20 Gy, 20-40 Gy, 40-60 Gy, and 60 Gy<.

Thyroid function assessment

Plasma thyroid-stimulating hormone (TSH) was routinely measured once every six months after RT for HNCs during follow-up examina-

Figure 1. Axial intensity modulated radiotherapy dosimetric plan without using thyroid constraints for patients with head and neck cancer.

tions. The patients' thyroid hormone levels were assessed at baseline using an immunoradiometric assay (IRMA) for TSH and radioimmunoassay (RIA) for FT4 (free thyroxine) before starting RT. In our hospital laboratory, the normal ranges of these values are: TSH: 0.3-4 mIU/L, FT4: 11.5-23.0 pmol/L. Hypothyroidism was categorized as euthyroid (normal TSH, normal FT4), subclinical HT (raised TSH, normal FT4), clinical HT (raised TSH with reduced FT4) or as central HT (reduced TSH, reduced FT4).

Statistical analysis

Statistical analyses of the data were conducted using IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Variables (age, sex, surgery, primary tumor site, staging, RT doses or addition of chemotherapy) possibly associated with the development of HT were tested using the independent sample t-test or Pearson's chi square test. In addition, logistic regression analysis was used to test for correlations among the variables. Descriptive statistics included determination of the mean, median, standard deviation, minimum and maximum. All p values less than 0.05 (two-tailed) were considered significant.

The study was approved by the local ethics committee of the institution (Ref: 2012/667). Written informed consent was obtained from all patients for thyroid hormone levels at follow-up examinations.

RESULTS

The present study included 90 patients (57 males, 33 females; mean age 52±13 years) who were treated with RT for HNCs. The histopathologic finding of 88 patients was squamous cell carcinoma, others were adenocystic carcinoma and undifferentiated carcinoma. The median follow-up of all patients after RT was 15 (range, 6-72) months. Additionally, the median follow-up period of patients with normal plasma TSH and FT4 level was 22.6 (range, 12-72) months.

Changes of thyroid hormone levels

Post-radiotherapy HT was found in 31 patients (34.4%). In this group, clinical and subclinical HT was present in eight (26%) and 23 (74%) patients, respectively (Table 1).

Time-interval for post-RT HT

The median time of onset for post-RT HT was eight (range, 6-31) months. Hypothyroidism was found in 16 patients (52%; n=31) at the 6-12 months' interval. Moreover, from these patients, 10 had subclinical and six had clinical HT. At the 12-18 months' interval, HT was detected in 10 patients (32%), which presented equally as clinical and subclinical. Hypothyroidism occurred in four patients (13%) at the 18-24 months' interval and each had subclinical HT. Subclinical HT was present in one patient (3%) after 30 months' follow-up.

Age and sex

Sex (57 males, 29.8% HT; 33 females, 30.3% HT) had no significant effect on HT development (p=0.59). Young age (<60 years, n=60, 35% HT; 60≤ years, n=30, 20% HT) was a significant risk factor for post-RT HT development (p=0.034).

Primary tumor site

Primary tumor sites were nasopharynx carcinoma (n=50), larynx (n=18), oral cavity (n=14), hypopharynx (n=2), oropharynx (n=4), salivary gland (n=2), respectively. Primary tumor site was not a significant risk factor for HT after RT (p=0.98).

Tumor staging

According to the TNM staging system of the AJCC; stage 1 was found in three patients (3%), stage 2 was found in 47 patients (52%), stage 3 was found in 34 patients (38%), stage 4 was found in six patients (7%). There were no significant effects of tumor staging for post-RT HT (p=0.33).

Table 1. Descriptive data and univariate analysis for categorical factors with evaluation of thyroid functions (n=90)

	Clinical HT	Subclinical HT	Euthyroid	*p*
Sex				=0.59
Male	5	13	39	
Female	3	10	23	
Age				=0.034
<60 years	2	22	36	
>60 years	4	3	23	
Primary tumor site				=0.98
Nasopharynx	3	15	32	
Larynx	4	4	10	
Oral cavity	-	1	13	
Hypopharynx	-	2	-	
Oropharynx	1	1	2	
Salivary gland	-	-	2	
Tumor, node, metastasis staging (AJCC)				=0.33
Stage I	-	-	3	
Stage II	4	11	32	
Stage III	3	10	21	
Stage IV	1	2	3	
Radiotherapy alone	2	1	7	=0.32
Radiotherapy with neck dissection	2	2	24	=0.75
Radiotherapy with chemotherapy	4	12	36	=0.23
MRD of primary tumor site				=0.32
60 Gy	2	4	27	
66 Gy	2	9	22	
70 Gy	4	10	10	
MRD of thyroid gland				=0.013
0-20 Gy	-	-	10	
20-40 Gy	1	2	6	
40-60 Gy	4	12	38	
>60 Gy	3	9	5	

HT: Hypothyroidism; AJCC: American Joint Committee on Cancer; MRD: Mean radiation dose.

Radiotherapy alone

Primary tumor and nodal site were treated with RT alone in 10 patients. In these patients, one had subclinical and two had clinical HT. There were no statistically significant differences in hormone levels in the RT-alone group (p=0.32).

Radiotherapy with surgery

Neck dissection (ND) was performed in 28 patients (31%), 16 of whom had unilateral ND and 12 had bilateral ND. Hypothyroidism was seen in one patient who underwent a unilateral ND, and in three patients who had bilateral NDs. Hypothyroidism was seen more frequently in bilateral ND than unilateral, but NDs had no significant contribution to the development of post-RT HT (p=0.75).

Radiotherapy with chemotherapy

Fifty-two patients (58%) were treated concomitant chemoradiotherapy (CRT). Hypothyroidism was detected in 16 patients (n=52; 31%) but this was not statistically significant (p=0.23).

Radiation doses

Total radiation doses were grouped into three levels: 66 Gy (n=33; 37%), 60 Gy (n=33; 37%) and 70 Gy (n=24; 26%). The mean total radiation dose was 66 Gy. In these parameters, the

distribution rate of HT was not statistically significant (p=0.32).

Mean radiation dose of thyroid gland was 52.2 Gy. 0-20 Gy was received in 10 patients (no HT); 20-40 Gy was received in nine patients, HT occurred in three patients (33.3%); 40-60 Gy was received in 54 patients, HT was present in 16 patients (30%); and 60 Gy< was received in 17 patients, HT occurred in 12 (70.5%) patients. A significant positive correlation was determined between radiation dose and HT incidence (p=0.013).

DISCUSSION

Radiotherapy is a curative treatment approach, which can be performed alone or with surgery and/or CT in the management of patients with HNC. Additionally, radiation to the neck can be considered for prophylactic or palliative management of HNCs. Although it is well known that RT induces thyroid functional changes and may induce different degrees of damage, it still represents a clinically underestimated problem.[4,7,8]

The etiology of post-RT HT includes vascular damage, parenchymal cell damage, and autoimmune reactions.[9,10] Fajardo et al.[11] have stated that damage to endothelial cells in thyroid capillary networks might be an important mechanism in both early and delayed radiation damage. Another hypothesis has reported that acute effects of RT depend on the balance between cell killing and compensatory replication of stem and proliferative cells. The development of late effects is due to the limited proliferative capacity of the stem cells affected by RT.[12]

In the present study, the incidence of HT was found as 34.4%, which is within the range of values (17-51%) reported in the literature.[3-6] This instability of the incidence ratios could be related to multiple variables such as age, sex, irradiation dose, surgery, concurrent chemoradiotherapy, and follow-up periods. Furthermore, subclinical HT (74%) constituted a higher portion of post-RT HT, and that was in agreement with some studies,[6,13] but contra to others[2,14] that found a higher proportion of clinical HT.

Overt hypothyroidism has been associated with cardiovascular disease. Whether subclinical HT and thyroid autoimmunity are also risk factors for cardiovascular disease is controversial. Hak et al.[15] have found that subclinical HT is a strong indicator of risk for atherosclerosis and myocardial infarction in elderly women. Therefore, timely treatment should be considered in an attempt to avoid adverse effects.[16]

The median time onset for post-RT HT was found as eight (range, 6-31) months in our analysis. In addition, 85% of HT cases were detected in the first 18 months after RT. Similarly, some studies reported that the median periods for development of HT were between eight and 16 (range, 1-96) months.[3,5,17] For this reason, these findings suggest that post-RT HT should be considered during the entire follow-up period, especially during the first 18 months.

The significant effect of MRT on the risk of post-RT HT was also reported in some studies.[3,5,6] In our study, The MRT independent of thyroid volume was 52.2 Gy. Differently, some studies reported that radiation dose-volumetric parameters could be a beneficial for post-RT HT.[3,5] Murthy et al.[3] found that only D100 (D100: mean dose to 100% of the thyroid gland) was a significant factor influencing HT in results related with dose-volumetric parameters of the thyroid gland. However, use of dose-volumetric parameters for post-RT HT has not been clearly identified and has inconsistent results.[3,5,18,19] Our result show that if the mean radiation dose received by the thyroid increases, it is a significant risk factor for post-RT HT, and this risk starts after 20 Gy. On the other hand, the mean radiation dose of the primary tumor site was 66 Gy and there was no statistically significant effect of post-RT, similar with the literature.[3,5,14,19]

There is also a debate about the correlation of age, sex, thyroid volume, neck dissection before RT, primary tumor site, and stage. For instance, some studies indicate a higher incidence of HT among female patients[1,7,20] whereas other studies show no impact on the likelihood of developing HT on the basis of sex.[13,17,21-23] Diaz et al.[19] reported that smaller thyroid volume had an increased risk factor for post-RT HT. Moreover, Alterio et al.[7] reported that women's thyroid glands were less affected by RT as they were smaller than men's. We found that sex did not correlate significantly with post-RT HT development. However, when we grouped the patients according to age above and below 60 years, we found that younger age was a significant risk fac-

tor for post-RT HT, as with other studies in the literature.[13,19,20] The increased efficacy of RT in younger patients who have a more mitotic activity may explain the greater incidence of HT in this group (<60 years).[24] However, the effect of age has been disproved by many researchers.[1,3,14,21,23] The difference of our study from others could be that age was analyzed in two groups (<60 years and ≥60 years).

Tumor staging is sometimes significantly associated with RT. Wu et al.[25] found that T_1 to T_2 tumors had a significant association with subclinical hypothyroidism. Another study showed that nodal positivity of the neck was a significant factor, but T classification and overall tumor stage was not. This result was attributed to high-dose treatment to the thyroid gland received during positive node irradiation.[3] Furthermore, Colevas et al.[22] found a trend toward decreased rating of HT in patients with clinic.

First stage T_1 or N_3, and for tumors located in the oral cavity.[22] The current study did not find tumor staging to be a significant factor for post-RT HT.

Interestingly, in our study, nasopharynx carcinoma had the highest rate (56%) of primary tumor and this could create a risk of central HT (characterized by insufficient TSH secretion resulting in low levels of thyroid hormones). Accordingly, Rønjom et al.[6] excluded patients with nasopharynx carcinoma in a study of post-RT HT, because they were concerned about the likely radiation effect on the pituitary gland and consequent occurrence of central HT. However, in our analysis results, we found no clues related with central HT. On the other hand, the effects of primary tumor site RT on the thyroid gland (e.g. carcinomas of larynx, oropharynx and hypopharynx) could be significant, because it is located in very close proximity to the target of irradiation.[3,13,26,27] Conversely, some studies found no association between HT and primary tumor site irradiation,[6,7,21] as in our study.

Some studies suggested that concurrent CT does not increase the risk of developing post-RT HT.[1,5,21,23,25] We confirmed their results; there was no difference between groups that developed more or less HT. Consequently, with the exceptions of age and MRT, there were no statistically significant differences found for several factors, including sex, primary site, TNM stage, neck dissection, and radiation dosage to the primary tumor site.

We accept that our study has some limitations. The median follow-up period of patients with normal plasma thyroid hormone levels was 22.6 months. However, many other literature reports suggest that longer follow-up (latency as late as 20 years has been reported by one study)[20] for these patients could be appropriate.[9,17,21,23,28] For this reason, the incidence ratio of our results for HT may be increased with longer follow-up.

Conclusion

In the present study, the common incidence of post-RT HT was 34.4% in patients with HNC who underwent RT alone or in combination with other procedures. Age younger than 60 years and increased MRT (especially mean thyroid doses 20 Gy<) were significant risk factors for post-RT HT. In addition, 85% of HT cases were detected in the first 18 months after RT. Physicians should be concerned about HT in the first 18 months after RT, especially in patients of younger age (<60 years) and who received a high MRT. We suggest that physicians should not neglect to evaluate thyroid function of patients with HNC in long-term follow-up when radiotherapy is included in the treatment protocol.

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