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ORIGINAL ARTICLE

Hypothyroidism after primary surgical treatment for laryngeal and hypopharyngeal cancer

Larenks ve hipofarenks kanserlerinde primer cerrahi tedavi sonrası hipotiroidizm

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Objectives: We investigated the incidence of hypothyroidism after treatment of laryngeal or hypopharyngeal cancer (LHC), and evaluated its relationship with treatment modalities.

Patients and Methods: Thyroid functions of 42 patients (41 males, 1 female; mean age 58 years; range 35 to 81 years) undergoing surgical treatment with (74%) or without adjuvant radiotherapy for LHC were prospectively evaluated preoperatively, on the 15th day, and in the sixth month postoperatively. The results were compared in relation to the treatment methods employed.

Results: The overall incidence of post-treatment hypothyroidism was 23.8%. Five patients had hypothyroidism in the early postoperative period, and this number increased to 10 after six months. All patients with hypothyroidism had undergone total laryngectomy with bilateral neck dissection, followed by radiotherapy. A significantly higher incidence of hypothyroidism was associated with total laryngectomy, bilateral neck dissection, level VI dissection, partial or bilateral thyroidectomy, adjuvant radiotherapy, and upper mediastinal radiotherapy.

Conclusion: The incidence of post-treatment hypothyroidism is not rare in LHC patients, requiring long-term monitoring of thyroid functions to prevent associated morbidities.

Key Words: Hypothyroidism/etiology; laryngeal neoplasms/surgery; laryngectomy; postoperative complications/etiology; risk factors; thyroid function tests.

Amaç: Larenks ve hipofarenks kanserlerinde (LHK) tedavi sonrası hipotiroidi görülme sıklığı araştırıldı ve uygulanan tedavi yöntemi ile hipotiroidi sıklığı arasındaki ilişki incelendi.

Hastalar ve Yöntemler: Cerrahi tedavi gören LHK'li 42 hastanın (41 erkek, 1 kadın; ort. yaş 58; dağılım 35-81) tiroid fonksiyonları ileriye dönük olarak, tedavi öncesinde, ameliyattan 15 gün ve altı ay sonra değerlendirildi. Hastaların %74'üne cerrahiden sonra adjuvan radyoterapi uygulandı. Sonuçlar uygulanan tedavi yöntemleriyle karşılaştırmalı olarak değerlendirildi.

Bulgular: Tedavi sonrası genel hipotiroidi oranı %23.8 bulundu. Ameliyat sonrası erken dönemde beş hastada hipotiroidi görülürken, altı ay sonra bu sayı 10'a yükseldi. Hipotiroidi gelişen tüm hastalarda total larenjektomi, iki taraflı boyun diseksiyonu ve ameliyat sonrası radyoterapi uygulanmıştı. Total larenjektomi, iki taraflı boyun diseksiyonu, seviye VI diseksiyon, kısmi veya iki taraflı tiroidektomi, adjuvan radyoterapi ve üst mediastinal radyoterapi uygulamalarının hipotiroidi gelişme sıklığı ile anlamlı ilişki gösterdiği saptandı.

Sonuç: Tedavisi sonrası hipotiroidi sıklığı LHK'li hastalarda yüksektir. Hipotiroidi morbiditesinden korunmak için, bu hastalar tiroid fonksiyon testleri ile tedavi sonrasında uzun süreli olarak izlenmelidir.

Anahtar Sözcükler: Hipotiroidizm/etyoloji; larenks neoplazileri/cerrahi; larenjektomi; ameliyat sonrası komplikasyon; risk faktörü; tiroid fonksiyon testleri.

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In spite of all efforts, there has been no increase in the survival rates of head and neck cancer in the last few decades, and most of the studies on this topic have focused on decreasing the morbidity associated with treatment and improving the quality of life. All modalities of cancer treatment have morbidities, some of which are preventable and treatable once they are diagnosed. One of such easily diagnosed and treated morbidities of treatment of laryngeal and hypopharyngeal cancer is hypothyroidism, which is often overlooked.[1,2]

High hypothyroidism incidence after treatment of laryngeal and hypopharyngeal cancer is not surprising due to close anatomic proximity of the thyroid gland to the larynx, hypopharynx, and cervical lymph nodes. The thyroid gland may easily be injured by direct or indirect trauma during treatment of primary laryngeal and hypopharyngeal tumor or neck.[3-5]

Hypothyroidism may be clinical or subclinical. Clinical hypothyroidism presents with high thyroid-stimulating hormone (TSH) and low free T_4 levels, and subclinical hypothyroidism, also known as reduced thyroid reserve, presents with high TSH and normal free T_4 levels. Not only clinical, but also subclinical hypothyroidism may increase the risk for numerous early and late complications such as delayed wound healing, malnutrition, prolonged mucosal and skin edema, difficulty for decannulation, constipation, sleepiness, dysphonia, depression, etc.[1-7]

There are several retrospective and a few prospective studies demonstrating a high incidence of hypothyroidism after treatment of laryngeal and hypopharyngeal cancer.[1-6,8] In 1961, Felix et al. reported the first case of hypothyroidism that occurred six years after treatment for laryngeal cancer.[3] Then Lavelle's[8] paper in 1971 is probably the first to report hypothyroidism associated with surgical therapy. The incidence of hypothyroidism varies from 8% to 67% in the literature.[1-6,9-15] Most of these cases were subclinical. It was also stressed that its incidence was related to the follow-up period and increased with a longer follow-up. It was assumed that this relation might be a result of scar formation and atrophy of the thyroid in the course of time.[9,11,16] Some authors also focused on the relation between hypothyroidism and treatment modality, namely, only surgery or radiotherapy, combined therapy, type of surgery directed to the primary tumor and neck, and field and dose of radiation therapy.[1-4,10-13,17]

The aim of this study was to determine the incidence of hypothyroidism after treatment of laryngeal and hypopharyngeal cancer, and to evaluate the relationship between the occurrence of hypothyroidism and treatment modality.

PATIENTS AND METHODS

Forty-nine patients with laryngeal or hypopharyngeal cancer were prospectively evaluated, who were primarily treated with surgery or surgery followed by radiotherapy in our institution from May 2002 to November 2003. Three patients who had thyroid dysfunction preoperatively, and four patients who had undergone total thyroidectomy as part of their surgical procedure were excluded from the study. Therefore, 42 patients (41 males, 1 female; mean age 58 years; range 35 to 81 years) were finally enrolled in the study.

Histopathology was squamous cell carcinoma in all cases. Primary tumor was located in the larynx in 93%, and in the hypopharynx in 7% of the patients. Clinically, only 21% of the patients had early stage disease, and 79% had advanced disease. Nearly half of the patients (55%) were N_0.

Treatment details are shown in Table I. Total laryngectomy was performed in 60% of the patients and neck dissection was performed in 88%, being bilateral in 29 patients (78%). Of all neck dissections (n=66), 44% were comprehensive. Level VI was dissected in only 14% of the patients. Partial thyroidectomy was performed in 38% of the patients, being unilateral in 56%. Adjuvant radiotherapy was administered to 74% of the patients, including the upper mediastinum in 26%. The dose of radiotherapy varied from 50 to 70 grays, depending on the indication. The patients having comprehensive bilateral neck dissection on one side and selective on the other side were considered in the comprehensive group while evaluating the relationship between the incidence of hypothyroidism and type of the neck dissection.

Antimicrosomal and antithyroglobulin antibodies were measured by the indirect fluorescent technique preoperatively and on the 15th postoperative day. The cut-off level of normal reactivity of the antimicrosomal and antithyroglobulin antibodies was accepted as 1:10, and a higher level was consid-

TABLE I
TREATMENT MODALITIES (n=42)

Treatment modality	n	%
Treatment of primary tumor		
Total laryngectomy	25	60
Partial laryngectomy	17	40
Treatment of neck		
Neck dissection (–)	5	12
Neck dissection (+)	37	88
Unilateral	8	22
Bilateral	29	78
Comprehensive	29	44
Selective	37	56
Dissection of zone VI		
Absent	36	86
Present	6	14
Partial thyroidectomy		
Absent	26	62
Present	16	38
Unilateral	9	56
Bilateral	7	44
Adjuvant radiotherapy		
Absent	11	26
Present	31	74
Upper mediastinum (+)	8	26
Upper mediastinum (–)	23	74

ered positive. Thyroid functions were measured by the ADVIA Centaur Immunoassay system preoperatively and on the 15th day and in the 6th month postoperatively. TSH levels higher than 5.50 mIU/ml accompanied by normal free T_4 levels (between 0.89 and 1.81 ng/dl) and by free T_4 lower than 0.89 ng/dl were accepted as subclinical and clinical hypothyroidism, respectively. All patients with hypothyroidism, either clinical or subclinical, were referred to the endocrinology department for hormone replacement therapy.

The procedures carried out were in accordance with the ethical standards of the World Medical Association (Declaration of Helsinki). Institutional review board approval and written informed consent of the patients were obtained. For statistical analysis, SPSS (Statistical Package for the Social Sciences for Windows, version 9.05, 1998) computer program, and likelihood chi-square and linear regression tests were used. P values equal to or less than 0.05 were accepted as statistically significant.

TABLE II
RELATION BETWEEN THE TREATMENT MODALITY AND HYPOTHYROIDISM INCIDENCE

Treatment modality	Hypothyroidism		
	n	%	*p*
Treatment of primary tumor			
Total laryngectomy (n=25)	10	40.0	
Partial laryngectomy (n=17)	–		<0.01
Treatment of neck			
Neck dissection (–) (n=5)	–		
Neck dissection (+) (n=37)	10	27.0	>0.005
Unilateral (n=8)	–		
Bilateral (n=29)	10	34.5	<0.05
Comprehensive (n=16)	4	25.0	
Selective (n=21)	6	28.6	>0.05
Dissection of zone VI			
Absent (n=36)	5	13.8	
Present (n=6)	5	83.3	<0.001
Partial thyroidectomy			
Absent (n=26)	2	7.7	<0.01
Present (n=16)	8	50.0	
Unilateral (n=9)	4	44.4	<0.01
Bilateral (n=7)	4	57.1	
Adjuvant radiotherapy			
Absent (n=11)	–		<0.01
Present (n=31)	10	32.3	
Upper mediastinum (+) (n=8)	8	26.0	<0.001
Upper mediastinum (–) (n=23)	23	74.0	

RESULTS

Three patients (6%) had thyroid dysfunction preoperatively and were excluded. Hypothyroidism was detected in 11.9% (5/42) on the 15th postoperative day and in 23.8% (10/42) in the sixth postoperative month. Hypothyroidism was subclinical in nine patients (21.4%) and one patient had clinical hypothyroidism (2.4%). Thus, 90% of the cases of hypothyroidism were subclinical.

Antithyroglobulin antibody was negative in all cases, either pre- or postoperatively. Antimicrosomal antibody was positive in three patients preoperatively, in two patients postoperatively; among them, only one patient had hypothyroidism.

Treatment modalities associated with hypothyroidism are shown in Table II. The incidence of hypothyroidism was significantly higher in patients undergoing total laryngectomy, bilateral neck dis-

sections, level VI dissection, partial thyroidectomy, bilateral thyroidectomy, adjuvant radiotherapy, and upper mediastinal radiotherapy. The incidence of hypothyroidism did not differ between patients with or without unilateral neck dissection (comprehensive or selective).

Risk factors for hypothyroidism as related to treatment modalities are shown in Figure 1. All the patients with hypothyroidism had total laryngectomy, bilateral neck dissections, and adjuvant radiotherapy. Almost all the patients had partial thyroidectomy (80%) and adjuvant radiotherapy (70%) including the upper mediastinum. Level VI dissection and bilateral partial thyroidectomy had been performed in half of the patients that developed hypothyroidism.

In univariate regression analysis, the risk for hypothyroidism was 12 times higher with partial thyroidectomy and 31 times higher with level VI dissection (Table III).

DISCUSSION

Hypothyroidism after treatment of laryngeal and hypopharyngeal cancer is not rare, and though it is generally considered not to be a major complication, its diagnosis is very important to reduce morbidity associated with the treatment. Diagnosis and treatment of hypothyroidism is very easy and we should always keep the risk for hypothyroidism in mind during follow-up. It is also possible that the patients with head and neck cancer also have thyroid dysfunction before the treatment.[1,7] The incidence of pretreatment thyroid dysfunction was 6% in our study. Two previous studies reported this rate as 6% and 11%, respectively.[1,7] These high incidence rates justify the need for preoperative thyroid function studies in all patients undergoing surgery for head and neck cancer.

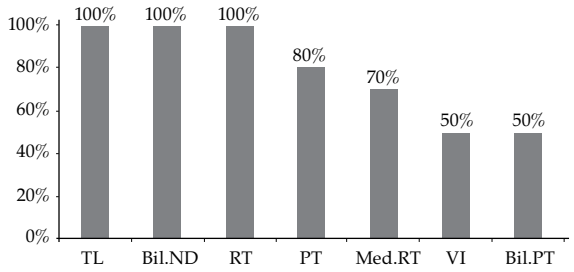

Fig. 1. *Risk factors in 10 patients for hypothyroidism related to treatment modalities. TL: Total laryngectomy; Bil.ND: Bilateral neck dissection; RT: Radiotherapy; PT: Partial thyroidectomy; Med.RT: Mediastinal radiotherapy; VI: Zone VI dissection; Bil.PT: Bilateral partial thyroidectomy.*

TABLE III
HYPOTHYROIDISM RISK FACTORS RELATED TO TREATMENT MODALITY IN UNIVARIATE REGRESSION ANALYSIS

Treatment modality	Significance	Exp (B)
Total laryngectomy	0.806	17986.40
Neck dissection	0.854	3675.644
Zone VI dissection	0.004	31.000
Partial thyroidectomy	0.005	11.999
Adjuvant radiotherapy	0.778	0

The overall incidence of hypothyroidism after treatment of head and neck cancer was reported between 8% and 67% in the literature.[1-6,9-15] Heterogeneity of study protocols such as the length of the follow-up period, definition of clinical and subclinical hypothyroidism, prospective or retrospective fashion, localization of cancer, and treatment modalities may account for this considerable difference between the results. Overall, the incidence of clinical and subclinical hypothyroidism after treatment of laryngeal and hypopharyngeal cancer in this prospective study was 23.8%. Literature reports and our findings demonstrate that hypothyroidism is not rare after the treatment of head and neck cancer and should not be overlooked.

Concerning the incidences of clinical and subclinical hypothyroidism reported in the literature,[2,3,5,10,13,15] subclinical hypothyroidism appears to have a higher incidence in most of the studies. Only de Jong et al.[10] and Tami et al.[3] reported equal rates for clinical and subclinical hypothyroidism. In our study, 90% of the patients with hypothyroidism had subclinical hypothyroidism. Hypothyroidism, whether clinical or subclinical, should always be treated because it increases the complication rate and morbidity of cancer treatment.[4,6,15] All of our patients with hypothyroidism were referred to the endocrinology department and all received hormone replacement therapy.

The length of follow-up is an important factor in the development of hypothyroidism, and it has been clearly demonstrated that its incidence increases with a longer follow-up period.[9,11,16,17] This may be due to scar formation and atrophy of the thyroid gland in the course of time. Mercado et al.[9] reported the incidences of hypothyroidism as 45% and 67% in the postoperative fourth and eighth years, respec-

tively. Colevas et al.[11] found the incidence of hypothyroidism as 45% in the postoperative second year, compared to 14% in the sixth postoperative month. Tell et al.[16] recommended life-long testing of thyroid functions after radiotherapy in patients with head and neck cancer. Garcia-Serra et al.[17] recommended that TSH be checked every six months for the first five years and yearly thereafter, regardless of clinical symptoms. Although the follow-up period was quite shorter in our study, the incidence of postoperative hypothyroidism almost doubled (from 11.9% to 23.8%) in six months. Regardless of the contribution postoperative radiation therapy makes to the increased incidence of hypothyroidism, all patients should be screened for a long time, probably a lifetime, after treatment of head and neck cancer.

Some studies suggested autoimmune reactions, in particular radiotherapy-induced reactions, as one possible mechanism of post-treatment hypothyroidism.[1,2,5] In these studies, high levels of antithyroglobulin and antimicrosomal antibodies in the postoperative period were associated with increased incidence of hypothyroidism. In contrast to these reports, pre- or postoperative antithyroglobulin antibody levels were negative in all our cases, and antimicrosomal antibody was positive in only two patients postoperatively; among them, only one patient had hypothyroidism.

It is also very important to know which treatment modality is associated with a higher incidence of hypothyroidism and to predict the patients at a greater risk for hypothyroidism. Vascular supply and parenchyma of the thyroid gland may be directly disturbed during surgical treatment of primary tumor and neck. These effects are closely related to the field of surgery. Compared to partial laryngectomy, Sinard et al.[1] and Aimoni et al.[2] reported a higher incidence of hypothyroidism in patients undergoing total laryngectomy. This was also the case in our study. We found no literature data linking the incidence of hypothyroidism with the type of neck dissection, such as comprehensive versus selective, and bilateral versus unilateral. Consistent with the findings of Sinard et al.,[1] unilateral neck dissection was not found as a risk factor for the development of hypothyroidism in our study. However, bilateral neck dissection was associated with a significantly higher incidence of hypothyroidism. The extent of neck dissection, whether comprehensive or selective, did not have an adverse effect on the incidence of hypothyroidism. On the other hand, zone VI dissections were significantly associated with the development of hypothyroidism. This result is not surprising, because vascular supply of the thyroid gland may be easily injured during zone VI dissections.

During surgical therapy of the primary tumor or neck for laryngeal and hypopharyngeal cancer, thyroidectomy may be required due to direct invasion of the gland by the tumor. Of course, hypothyroidism is inevitable after total thyroidectomy. Therefore, four of our patients who had undergone total thyroidectomy as part of their surgical therapy were excluded from this study. Partial thyroidectomy has been reported to be a risk factor for hypothyroidism in some studies.[1,4,8,14,15] The results of our study support these findings, especially when partial thyroidectomy is bilateral. In univariate regression analysis, we found that hypothyroidism risk increased 12 times after partial thyroidectomy, and 31 times after zone VI dissection.

Early cases of hypothyroidism appear to be related to radiation treatment. Vascular supply and parenchyma of the thyroid gland may also be indirectly disturbed by radiation therapy of primary tumor and neck for laryngeal and hypopharyngeal cancer. Fibrosis, scar formation, and autoimmune reactions in the thyroid gland secondary to radiotherapy may be the reasons of hypothyroidism. The first reported case concerning the development of hypothyroidism following treatment was related to radiotherapy for laryngeal cancer.[3] Radiotherapy, either primary or adjuvant, is considered to be a risk factor for hypothyroidism in several studies.[1-3,13] Our results also supported these data. In our opinion, the field of radiotherapy is also another important factor as the field of surgical treatment. However, no data exist concerning radiotherapy including the upper mediastinum. Jong et al.[10] reported the field of radiotherapy as the area under the cricoid cartilage. Garcia-Serra et al.[17] stressed that radiotherapy delivered to the thyroid region at doses of 50 Gy or higher resulted in biochemical evidence for primary hypothyroidism in at least 50% of the patients. We also found that the field of radiotherapy including the upper mediastinum was a statistically significant risk factor for hypothyroidism. Additionally, Colevas et al.[11] noted that total dose and fractionation of radiotherapy were important criteria on the effect of radiotherapy on hypothyroidism. In our study, we could not evaluate these parameters due to the small number of patients in each group.

Combination of surgery and radiotherapy causes hypothyroidism more frequently compared to surgery or radiotherapy alone.[1,4,6,10,12-15] All of our patients with hypothyroidism had undergone total laryngectomy, bilateral neck dissection, and adjuvant radiotherapy. Hence, literature reports and the results of our study show that patients undergoing combined therapy have the highest risk for hypothyroidism.

From our findings, the following conclusions were drawn:

1- The incidence of hypothyroidism after the treatment of laryngeal and hypopharyngeal cancer is not low; and hypothyroidism, especially subclinical hypothyroidism, should not be overlooked. The incidence of subclinical hypothyroidism in our series was 23.8%, in other words, about one-fourth of the patients.

2- The incidence of hypothyroidism may increase in the course of time. Therefore, all patients treated for laryngeal or hypopharyngeal cancer should undergo routine screening for hypothyroidism during the follow-up period, which may be life-long.

3- Even subclinical hypothyroidism should be treated by hormone replacement therapy.

4- Hypothyroidism may be a result of direct or indirect injury to the vascular supply and parenchyma of the thyroid gland by surgical or radiation therapy directed to the primary tumor or neck. Autoimmune reactions do not seem to play a role in the development of post-treatment hypothyroidism.

5- Risk factors for the development of post-treatment hypothyroidism include total laryngectomy, bilateral neck dissection (especially including zone VI), partial thyroidectomy (especially bilateral), and adjuvant radiotherapy (especially including the upper mediastinum). Among these, zone VI dissection and partial thyroidectomy have the strongest effect on hypothyroidism. Combined therapy including surgery plus radiotherapy, which is frequently used for advanced carcinoma of the larynx or hypopharynx, is a major risk factor for the development of post-treatment hypothyroidism.

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