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Original Article *Özgün Araştırma*

A CROSS-SECTIONAL STUDY OF THE ACUTE EFFECTS OF HEAD AND NECK RADIOTHERAPY ON THE THYROID VOLUME AND FUNCTION

Baş ve Boyun Radyoterapisinin Tiroid Volümü ve Fonksiyonu Üzerine Akut Etkileri Üzerine Kesitsel Bir Çalışma

Fevziye İlknur KAYALI[1], Uğur TOPRAK[2], Rahşan HABİBOĞLU[3]

[1,3] Ankara Şehir Hastanesi Radyasyon Onkolojisi Bölümü, ANKARA, TÜRKİYE
[2]Eskişehir Osman Gazi Üniversitesi Tıp Fakültesi, Radyoloji Departmanı, ESKİŞEHİR, TÜRKİYE

ABSTRACT

Objective: To evaluate the acute effects of radiotherapy on the volume and function of the thyroid gland.

Material and Methods: Thirty-one patients with head and neck cancer were included in the study. Patients with thyroid cancer or thyroidectomy were excluded. There was no patient for whom radiotherapy was the only tretment modality. Thyroid function tests, thyroglobulin and thyroid volume imaging were evaluated before and immediately after radiotherapy,

Results: After radiotherapy 13 patients had dysfunction. Among 13, 8 had subclinical hyperthyroidism, 1 had clinical hyperthyroidism, 1 had subclinical hypothyroidism and 3 developed clinical hypothyroidism. After chemoradiotherapy all patients had significantly decreased FT3 ($p<0.001$). FT4 slightly increased in all of the patients other than operated patients ($p>0.05$). After treatment, the TSH decreased in patients who were not operated but given chemotherapy whereas it was increased in patients who were operated but not given chemotherapy ($p>0.05$). The thyroid volume was unchanged in 2 patients, decreased in 17 patients and increased in 12 patients ($p>0.05$). There was no correlation between chemotherapy or surgery, and the volume of the thyroid gland. No thyroiditis was seen in the acute phase.

Conclusion: Hyperthyroidism appeared immediately after radiotherapy. The volume of the gland starts to be slightly affected in the acute phase. Due to possible clinical thyroid dysfunction, after completion of the radiotherapy patients should not be discharged without thyroid function tests.

***Keywords**: Head and neck cancer, radiotherapy, thyroid disfunction*

ÖZ

Amaç: Radyoterapinin tiroid bezinin volümü ve işlevi üzerindeki akut etkilerini değerlendirmek.

Gereç ve Yöntemler: Çalışmaya baş boyun kanserli 31 hasta alındı. Tiroid kanseri veya tiroidektomili hastalar çalışma dışı bırakıldı. Radyoterapinin tek tedavi modalitesi olarak uygulandığı hiçbir hasta yoktu. Radyoterapiden hemen önce ve sonra tiroid fonksiyon testleri, tiroglobulin ve tiroid volüm görüntüleme yapıldı.

Bulgular: Radyoterapi sonrası 13 hastada disfonksiyon mevcuttu. On üç hastanın 8'inde subklinik hipertiroidi, 1'inde klinik hipertiroidi, 1'inde subklinik hipotiroidi ve 3'ünde klinik hipotiroidi vardı. Kemoradyoterapi sonrası tüm hastalarda anlamlı olarak azalmış FT3 mevcuttu ($p<0.001$). FT4, opere edilen hastalar dışındaki tüm hastalarda hafifçe artmış olarak saptandı ($p>0.05$). Tedavi sonrası, TSH, kemoterapi verilen ve opere edilmemiş hastalarda azalmışken, opere edilen ve kemoterapi verilmeyen hastalarda artmış olarak saptandı ($p>0.05$). İki hastada tiroid hacmi değişmedi, 17 hastada azaldı ve 12 hastada arttı ($p>0.05$). Kemoterapi veya cerrahi işlem ile tiroid bezinin hacmi arasında korelasyon yoktu. Akut fazda tiroidit görülmedi.

Sonuç: Hipertiroidinin radyoterapiden hemen sonra ortaya çıktığı sonucu gözlendi. Akut fazda bez hacmi hafifçe etkilenmeye başlar. Muhtemel klinik tiroid fonksiyon bozukluğu nedeniyle, radyoterapi tamamlandıktan sonra hastalar tiroid fonksiyon testleri yapılmadan taburcu edilmemelidir.

***Anahtar Kelimeler**: Baş-boyun kanseri, radyoterapi, tiroid disfonksiyonu*

Correspondence / Yazışma Adresi: **Dr. F. İlknur KAYALI**
Ankara Şehir Hastanesi Radyasyon Onkolojisi Bölümü MHC Blok Bilkent, ANKARA, TÜRKİYE
Phone / Tel: +90 *539 8447558* **E-mail /** E-posta: ilknurkayali@yahoo.com
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ORCID NO: [1]0000-0002-0649-115X, [2]0000-0002-1244-2485 [3]0000-0002-3658-1164

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INTRODUCTION

Early stage head and neck cancer can be treated by radiotherapy alone however, in advanced stages it is used with surgery and/or chemotherapy. During radiotherapy the thyroid gland is partially or completely irradiated. In fact, because of the relatively low proliferative index of the thyroid gland cells, the organ is resistant to radiation (1). However, it is known that the radiation affects the morphology of the thyroid gland and induces thyroid dysfunction, thus radiation induced hypothyroidism, hyperthyroidism, adenoma, Graves' disease and thyroid cancer may develop (2,3). Furthermore, it is believed that concomitant chemotherapy causes hypothyroidism by increasing the sensitivity of the gland to radiation (4). In contrast, there are studies reporting that chemotherapeutics in head and neck cancers do not affect the thyroid functions (5-7).

The etiology of radiation induced thyroid dysfunction depends on vascular and follicular cell injury and autoimmune reactions (8). However, the precise mechanism of the radiation injury is still not clear (9). In studies conducted to reveal these mechanisms, the methods used are mostly thyroid function tests, and radiological imaging methods (10, 11). Most of the studies have been conducted late after radiotherapy and retrospectively. Only a few studies were carried out on patients undergoing radiotherapy and/or in the period immediately after the treatment (11-13). However, in these studies the effects of radiotherapy or other concomitant treatments on the volume of the thyroid gland were not studied. Therefore, this study aims to evaluate the acute effects of radiotherapy with chemotherapy and/or surgery on the volume and function of the thyroid gland.

MATERIALS AND METHODS

Study Design

Data regarding head and neck cancer patients who underwent neck radiotherapy between 2012 and 2013 in Ankara Numune Training and Research Hospital Radiation Oncology Clinic were collected. This study was based on a retrospective analysis and received approval by local Ethical Committee (Date: 03.10.2019, desicion number: E-19-013). The study sample consisted of 31 patients with head and neck cancers. There was no patient for whom radiotherapy was the only treatment modality. The patients were staged according to the TNM staging system and their characteristics are presented in Table 1. The patients were grouped as operated/non-operated and chemotherapy-receiving/non-receiving.

Table 1: Patient Characteristics

Variable	**n (%)**
Gender	
Male	29 (93.56)
Female	2 (6.44)
TNM T Stage	
Carcinoma in-situ	1 (3.22)
T1	3 (9.66)
T2	9 (28.98)
T3	8 (25.76)
T4	9 (28.98)
Tx	1 (3.22)
TNM N Stage	
Nx	1 (3.22)
N0	21 (67.62)
N1	4 (12.88)
N2	4 (12.88)
Surgery	
Yes	12 (38.64)
No	19 (61.18)
Chemotherapy	
Yes	13 (41.86)
No	18 (58.14)

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The exclusion criteria were thyroidectomy and usage of thyroid hormones or medicines affecting the thyroid hormone levels.

Radiotherapy

Radiotherapy was given to all of the patients. The neck region, including the thyroid gland was irradiated.

The thyroid gland was entirely within the irradiation field. This was confirmed with the planning films. The total median dose applied was 63 Gy (42.4–70 Gy). A 2 Gy/ fraction was applied daily, 5 times a week.

Chemotherapy

Radiotherapy and concomitant chemotherapy were applied in 13 (41.86%) patients. Twelve patients received 30 mg/m2 of cisplatin weekly, one patient received 180 mg/m2 of cisplatin for every 3 weeks.

Surgery

Twelve (38.64%) patients had undergone surgery. A total laryngectomy had been performed on one of the patients, supraglottic laryngectomy and neck dissection on one patient, total laryngectomy with neck dissection on nine patients, and a malignant tumor excision of the oral base had been carried out on one patient.

Thyroid Function Tests

Before and and immediately after radiotherapy, thyroid stimulating hormone (TSH) (reference values 0.34–4.25 μIU/mL), free triiodothyronine (FT3) (reference values 2.5–3.9 pg/ml), free thyroxine (FT4) (reference values 0.61–1.2 ng/dl) levels were evaluated. Thyroglobulin antibody level (reference values 0–115 IU/mL) was evaluated for thyroiditis.

Conditions with normal TSH and thyroid hormone values were determined as ‘euthyroidism’; those with high TSH, low thyroxine values as ‘clinical hypothyroidism’; with high TSH and normal thyroxine values as ‘subclinical hypothyroidism’; with low TSH and high thyroxine values as ‘hyperthyroidism’ and with low TSH and normal thyroxine values as ‘subclinical hyperthyroidism’.

Ultrasonography

The thyroid ultrasonography was performed with GE Logiq 9 ultrasonography device (General Electric Medical Systems; Milwaukee, WI, USA) using 12 and 7 MHz linear multifrequency probes in realtime. The ultrasonography was performed before and immediately after the radiotherapy was completed. The volume of the thyroid gland was calculated with the ellipsoid formula: (Volume (ml) = length (cm) x width (cm) x thickness (cm) x 1/6 π).

Statistical Analysis

Data analysis was carried out with statistical software (SPSS, version 18; 2009, Chicago, Ill, USA). The descriptive statistics for the demographic characteristics of the patients are given as mean ± standard deviation (SD). The patients were grouped as operated versus non-operated and chemotherapy receiving versus non-receiving. In addition to radiotherapy, the effects of surgery and chemotherapy on the thyroid gland were researched. The comparison of the pre-treatment and post-treatment values according to the groups was obtained with repeated measurements using two-way variant analysis (two-way ANOVA test). $p<0.05$ was found to be statistically significant.

RESULTS

Mean patient age was 58 years (range: 36-76 years). Before initiation of radiotherapy, 7 patients were found to have subclinical thyroid dysfunction. Of these 7 patients 6 had subclinical hyperthyroidism and 1 had subclinical hypothyroidism. Before the radiotherapy none of the patients had clinical thyroid dysfunction. After the treatment, 3 of the 6 subclinical hyperthyroidism patients were found to be euthyroid while the patient with subclinical hypothyroidism remained the same, thus in 4 patients the dysfunction continued.

After completion of the therapy, there were 13 patients with thyroid dysfunction, 3 with previously existing subclinical hyperthyroidism, 1 with previously

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existing subclinical hypothyroidism, 8 with newly developed subclinical hyperthyroidism and 1 with clinical hyperthyroidism. The most common thyroid disfunction was subclinical hyperthyroidism.

The changes in thyroid function tests are given in Table 2. After treatment, all patients showed a significant decline in FT3 levels ($p<0.0001$). The post-treatment FT3 levels decreased more in those patients receiving chemotherapy ($p=0.007$). There was no significant difference in FT3 levels in the operated versus non-operated patients.

The total number of patients with thyroid dysfunction after the treatment was 13 (41.86%) with 9 (69%) having newly developed dysfunction.

While slightly decreased in the patients who had undergone surgery, the FT4 was slightly increased in all of the patients. However, these differences were not statistically significant ($p>0.05$).

After the treatment, there was a decrease in TSH levels in patients receiving chemotherapy and in non-operated patients. TSH was increased in patients who had surgery, who did not receive chemotherapy and also on average over the whole study group. However, these differences were not significant ($p > 0.05$).

After the treatment, there was no change in the volume of the thyroid gland in 2 patients (6%), decrease in 17 patients (55%) and increase in 12 patients (39%). However, pre-treatment and post-treatment differences were not significant. No relation between chemotherapy or surgery and the thyroid volume was found. (Table 3) According to the thyroglobulin antibody titers or the US, no thyroiditis was found in any of the patients.

Although decrease in FT3 was statistically significant, the increase in FT4 caused subclinical hyperthyroidism.

Table 2: Pre-and post-treatment changes in thyroid function tests

	FT3 (pg/ml)		**FT4 (ng/ml)**		**TSH (µIU/mL)**	
	Mean±SD	p value	Mean±SD	p value	Mean±SD	p value
Operated						
Before	2.70±0.45	0.0001	1.01±0.25	0.410	5.95±15.15	0.660
After	2.16±0.56		0.89±0.20		8.15±23.20	
Non-operated		0.0004				
Before	2.82±0.46		1.01±0.26	0.598	1.05±0.55	0.194
After	2.32±0.58		1.05±0.33		0.84±0.70	
Chemotherapy						
Before	2.93±0.51	<0.0001	1.01±0.26	0.675	1.04±0.56	0.074
After	1.96±0.50		1.04±0.30		0.75±0.69	
Non-Chemotherapy						
Before	2.67±0.38	0.007	0.90±0.24	0.462	4.32±12.41	0.721
After	2.47±0.52		0.95±0.29		5.78±18.98	
Total				0.563		
Before	2.78±0.45	0.0002	0.95±0.25		2.94±9.49	0.815
After	2.26±0.57		0.99±0.29		3.67±14.50	

Table 3: Pre-and post-treatmentchanges in thyroid volume (cm^3)

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	Before	After	P value
Operated	18.17±8.20	18.13±11.60	NS
Non-operated	14.12±8.23	13.22±8.22	NS
Chemotherapy	18.53±7.58	17.73±11.19	NS
Non-Chemotherapy	15.22±8.77	15.15±10.27	NS
Total	16.61±8.32	16.23±10.56	NS

p=not significant.

DISCUSSION

There are several studies related to thyroid dysfunction in the late period after the radiotherapy in patients with head and neck cancers (1-10,14,15). Most of the studies showed that hypothyroidism developed and worsened over time (16,17). Imaging studies showed that the thyroid dimensions decreased over time (10). However, studies showing the acute effects during and right after radiotherapy are limited (11-13). It is reported that the acute effects in the thyroid gland arise from injury to the parenchymal cells (18). It has been recorded that the first effect was a type of thyrotoxicosis involving a period up to 4 weeks after the treatment. These studies showed that radiotherapy increases the thyroid gland hormone secretion, thus decreasing the TSH levels through a negative feedback mechanism. In the present study, post-treatment hyperthyroidism was seen in 9 of the 13 patients (8 cases being subclinical). TSH was decreased in the patients receiving chemotherapy and non-operated patients.

FT4 is the most sensitive marker of thyroid dysfunction induced by radiotherapy (18). As a result of the parenchymal injury FT4 levels increase causing subclinical or clinical hyperthyroidism. It is claimed that radiotherapy induced thyroid toxicity is underestimated and underreported (2). The study which had the purpose to examine thyroid dysfunction in the early phase of radiotherapy to the head and neck region by Koc et al., showed that 3 of 28 patients who had undergone surgery and 2 out of 19 patients who were not operated had early hyperthyroidism (12). In the present study, the non-operated patients and the whole study group had slightly elevated FT4 levels. Eight of 13 patients (62%) developed subclinical hyperthyroidism and one of thirteen patients (8%) developed clinical hyperthyroidism. The patient with clinical hyperthyroidism was given only radiotherapy without concomitant chemotherapy after surgical treatment. No clinical hyperthyroidism was reported in earlier studies (11-13). In the present study the most common thyroid dysfunction was subclinical hyperthyroidism (25.76%). Most of these patients, 5/8 (63%), had received chemotherapy.

A significant decrease in FT3 levels was reported in two studies concerning the acute phase of radiotherapy (12,13). However, in another study FT3 levels had not changed (11). In the present study, after the treatment FT3 levels had significantly decreased in each group. It is interesting that FT3 levels decreased more in patients receiving chemotherapy than in the patients who had not received chemotherapy.

There are few studies that have investigated the effects of chemotherapy on the thyroid gland. Some chemotherapy agents (e.g. 5-fluorouracil, L-asparaginase) and anti-oestrogens (tamoxifen) were reported to affect the thyroid hormone levels (4,19) although, other researchers reported that the chemotherapy combinations in head and neck tumors did not affect the thyroid functions (5-8,11,13,20,21). In the current study, 6 of 13 patients (46%) developed thyroid dysfunction after receiving chemotherapy. Of the 8 patients with subclinical hyperthyroidism, 5 (63%), were receiving chemotherapy. The decrease in

FT3 levels was more pronounced in the patients receiving chemotherapy. Even though it was statistically insignificant, an increase in FT4 and decrease in TSH were seen. These findings might indicate that chemotherapy increases cell injury. Bethge et al. did not observe any occurrence of hypothyroidism in lymphoma patients treated with chemotherapy alone, and the incidence of this complication was 34% with either radiotherapy alone or as part of combined therapy (22). Although chemotherapy alone does not have an effect, it is thought that in particular, concomitant chemoradiotherapy causes hypothyroidism by increasing the sensitivity of the thyroid to radiation (4). This indicates that studies including the early post-treatment period are needed.

In previous studies, either patients with thyroid dysfunction before radiotherapy were excluded or their pre-treatment status was unknown (23). In the current study, patients with pre-treatment subclinical dysfunction were included and they were asymptomatic. Although we had a small number of patients, we were able to observe the changes in patients with dysfunction. Seven patients (22.54%) had pre-treatment thyroid dysfunction. Six (19.32%) had subclinical hyperthyroidism and one (3.22%) had subclinical hypothyroidism. Three of the six subclinical hyperthyroidism patients became euthyroid after the treatment. The three patients with subclinical hyperthyroidism and the one with subclinical hypothyroidism remained unchanged.

Generally, late occurring and worsening, most commonly radiotherapy related dysfunction is hypothyroidism. The incidence rates of subclinical hypothyroidism in the 1st, 2nd and 3rd year after radiotherapy are 23.4%, 39.9% and 53.3% respectively (16). On average, hypothyroidism develops 1.4 years after treatment (24). In the retrospective series the earliest post-treatment hypothyroidism developed 4-6 weeks after treatment (7, 24-26). In the current study, hypothyroidism was seen in 4 patients (12.9%) (3 clinical and 1 subclinical hypothyroidism) after completion of the treatment. In the study by Koc et al., subclinicall hypothyroidism in the early period was seen in 14.0% of the patients (12). In the current study and that of Koc et al., the range of hypothyroidism in operated/non-operated patients was similar. While in patients who had received surgery, the FT4 level decreased and the TSH had increased. These changes were statistically non-significant. This seems to suggest that any surgical manipulation of the neck (e.g. neck dissection, translocation of the thyroid gland during laryngeal and proximal tracheal extirpation) may adversely affect thyroid functions. It is postulated that this might occur due to trauma or partial devascularization of the gland with transient and possibly permanent metabolic hypoactivity (3).

One of the etiologies of thyroid damage related to radiotherapy are autoimmune reactions. Antithyroglobulin titers were in turn related to radiation exposure (27). The measurement of antithyroid peroxidase, anti-thyroglobulin, and thyroid stimulating antibodies is useful in the diagnosis of thyroiditis and other thyroid dysfunctions (2). Ultrasound can show the reduced thyroid volume and structural changes (28). Some authors reported the development of hypothyroidism and thyroiditis in the first trimester after treatment (18). Although, in a recent study where thyroiditis was detected with US, it was reported that this condition developed during the treatment (11). However, in the present study thyroiditis was not detected neither with antibody titers nor with US findings.

It is known that the volume of the thyroid gland decreases later after the treatment however, in earlier studies, the changes in the volume of the thyroid gland, in the acute period, had not been researched. In the current study, after completion of the treatment the volume of the thyroid gland had not changed in 2 (6%) patients, decreased in 17 patients and increased in 12

(39%) patients (10). No relation was found between the volume of the thyroid and chemotherapy or surgery, meaning that the volume of the thyroid starts showing changes in the acute phase at the same time as the changes of the functions of the gland. However, these changes maybe in the form of an increase or decrease and the factors affecting these changes are yet to be discovered. Since there were a limited number of patients in the study, the changes of the tumor stage and sonographic findings according to age and gender were not evaluated.

Thyroid dysfunction, which is seen after radiotherapy in particular, is hypothyroidism. Unlike previous studies, it was found in our study that subclinical hyperthyroidism can be seen right after initiation of therapy. Also, it was found in our study that concomitant chemotherapy has effects on thyroid dysfunction. Furthermore, no thyroiditis was found in patients at the end of the treatment. It was observed that thyroid volume was affected immediately after the treatment. Since it is possible that clinical thyroid dysfunction can occur at the end of the treatment, patients having completed treatment should not be discharged from hospital without thyroid function testing.

Limitation of the study was being from a single institution thus a small number of patients were included. The data are preliminary and need to be validated by a larger number of patients.

REFERENCES

1. Hall EJ, Giaccia AJ. Radiobiology For The Radiologist. 7th ed. Philadelphia. JB Lippincott Co., 1994.
2. Jereczek-Fossa BA, Alterio D, Jassem J, Gibelli B, Tradati N, Orecchia R. Radiotherapy-induced thyroid dysfunctions. Cancer Treat Rev. 2004;30(4):369-84.
3. Miller M, Agrawal A. Hypothyroidism in post radiation head and neck cancer patients. Incidence, complications, and management. Curr Opin Otolaryngol Head Neck Surg. 2009;17(2):111-5.
4. Bajorunas DR, Ghavimi F, Jereb B, Sonenberg M. Endocrine sequelae of antineoplastic therapy in childhood head and neck malignancies. J Clin Endocrinol Metab.1980;50(2):329-35.
5. Posner MR, Ervin TJ, Miller D, Fabian RL, Norris CM Jr, Weichselbaum RR et al. Incidence of hypothyroidism following multimodality treatment for advanced squamous cell cancer of the head and neck. Laryngoscope. 1984;94(4):451-4.
6. Weissler MC, Berry BW. Thyroid stimulating hormone levels after radiotherapy and combined therapy for head and neck cancer. Head Neck. 1991;13(5):420-3.
7. Sinard RJ, TobinEJ, Mazzaferri EL, Hodgson SE, Young DC, Kunz AL et al. Hypothyroidism after treatment for nonthyroid head and neck cancer. Arch Otolaryngol Head Neck Surg. 2000;126(5):652-7.
8. Bhandare N, Kennedy L, Malyapa RS, Morris CG, Mendenhall WM. Primary and central hypothyroidism after radiotherapy for head-and-neck tumors. Int J Radiat Oncol Biol Phys. 2007;68(4):1131-9.
9. Hancock SL, McDougall IR, Constine LS. Thyroid abnormalities after therapeutic external radiation. Int J Radiat Oncol Biol Phys. 1995;31(5):1165-70.
10. Miller-Thomas MM, Kumar AJ, Sellin RV, Azimpoor S, Ang KK. The shrinking thyroid: how does thyroid size change following radiation therapy for laryngeal cancer? Am J Neuroradiol. 2009;30(3):613-6.
11. Bakhshandeh M, Hashemi B, Mahdavi SR, Nikoofar A, Edraki HR, Kazemnejad A. Evaluation of Thyroid Dysfunctions During Head-and-Neck Radiotherapy by Using Functional Analysis and

Ultrasonography. Int J Radiat Oncol Biol Phys. 2012;83(1):198-203.

12. Koc M, Unuvar N, Sen RC, Capoglu I, Sen M. A prospective evaluation of early thyroid dysfunction on completion of neck radiotherapy. Oral Oncol. 2003;39(6):597-600.
13. Koc M, Capoglu I. Thyroid dysfunction in patients treated with radiotherapy for neck. Am J Clin Oncol. 2009;32(2):150-3.
14. Shyh-An Y. Radiotherapy for Head and Neck Cancer. Semin Plast Surg. 2010;24(2):127-36.
15. Lin Z, Yang Z, He B, Wang D, Gao X, Tam SY et al. Pattern of radiation-induced thyroid gland changes in nasopharyngeal carcinoma patients in 48 months after radiotherapy. PLoSOne. 2018;13(7):e0200310.
16. 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. 2010;77(2):468-76.
17. Das TK, Das P, Das S, Jana A, Gupta P, Gupta P. A prospectivestudy of radiation- induced hypothyroidism in head and neck cancer patients. Tapas International Journal of Medical Science and Public Health. 2018;10(7):814-8.
18. Nishiyama K, Kozuka T, Higashihara T, Miyauchi K, Okagawa K. Acute radiation thyroiditis. Int J Radiat Oncol Biol Phys. 1996;36(5):1221-4.
19. Colevas AD, Read R, Thornhill J, Adak S, Tishler R, Busse P et al. Hypothyroidism incidence after multimodality treatment for stage III and IV squamous cell carcinomas of the head and neck. Int J Radiat Oncol Biol Phys. 2001;51(3):599-604.
20. Smith GL, Smith BD, Garden AS, Rosenthal DI, Sherman SI, Morrison WH et al. Hypothyroidism in older patients with head and neck cancer after treatment with radiation: a population-based study. Head Neck. 2009;31(8):1031-8.
21. Celik M, Meral R, Kanliada D, Aydemir L, Basaran B, Kiyak E. Post-radiotherapy hypothyroidism in head and neck cancers: When should we be concerned. Kulak Burun Bogaz Ihtis Derg. 2017;27(6):269-75.
22. Bethge W, Guggenberger D, Bamberg M, Kanz L, Bokemeyer C. Thyroidtoxicity of treatment for Hodgkin's disease. Ann Hematol. 2000;79(3):114-8.
23. Srikantia N, Rishi KS, Janaki MG, Bilmagga RS, Ponni A, Rajeev AG et al. How common is hypothyroidism after external radiotherapy to neck in head and neck cancer patients? Indian J Med Paediatr Oncol. 2011;32(3):143-8.
24. Aich RK, Ranjan DA, Pal S, Naha BL, Amitabh R. Iatrogenic hypothyroidism: a consequence of external beam radiotherapy to the head and neck malignancies. J Cancer Res Ther. 2005;1(3):142-6.
25. Turner SL, Tiver KW, Boyages SC. Thyroid dysfunction following radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 1995;31(2):279-83.
26. Cannon CR. Hypothyroidism in head and neck cancer patients: experimental and clinical observations. Laryngoscope. 1994(11);104:1-21.
27. LoGalbo AM, de Bree R, Kuik DJ, Lips PT, Mary B, VonBlomberg E et al. The prevalence of hypothyroidism after treatment for laryngeal and hypopharyngeal carcinomas: are autoantibodies of influence? Acta Otolaryngol. 2007;127(3):312-7.
28. Ricardi U, Corrias A, Einaudi S, Genitori L, Sandri A, diMontezemolo LC et al. Thyroid dysfunctionas a late effect in childhood medulloblastoma: a comparison of hyperfractionated versus conventionally fractionated craniospinal radiotherapy. Int J Radiat Oncol Biol Phys. 2001;50(5):1287-94.