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The Progress of Thyroid Cancer in The Covid 19 Period

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Research Article

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ABSTRACT

Objective: To evaluate the effect of the COVID-19 pandemic on the thyroid cancer stage.
Methods : Our study includes a comparative analysis of two patient groups treated for thyroid cancer. Patients who were treated for thyroid cancer between 11 April 2018 and 11 March 2020 were included in Group 1, and patients who were treated for thyroid cancer between 11 March 2020 and 11 February 2022 during the COVID-19 epidemic were included in Group 2.
Results: Groups 1 and 2 included 163 and 117 patients, respectively. Patients with preoperative fine-needle aspiration biopsy (FNAB) as potentially malignant or malignant were significantly higher in Group 2 (p=0.001). When compared according to the postoperative pathological diagnoses, there was a significant difference between the groups, poorly differentiated thyroid cancer was more common in Group 2 (p=0.018). Pathological tumour diameter was significantly larger in Group 2 (p=0.001).
Conclusions: Patients with suspicious findings in terms of thyroid diseases and cancer applied to the hospital later, both because of the fear of contracting COVID-19 and as a result of the pandemic measures recommended and implemented by all world health authorities. These patients applied to the hospital with their complaints gradually increasing in the following periods, parallel to this, there was a delay in the diagnosis of thyroid cancer and the disease could be detected at a more advanced stage.

Keywords: COVID-19, thyroid cancer, surgery

Covid 19 Döneminde Tiroid Kanserinin Seyri

Süreç

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ÖZ

Amaç: Bu çalışmadaki amacımız, COVİD-19 pandemisinin tiroid kanserinin evresine olan etkisini araştırmaktır.
Yöntem: Çalışmamız, tiroid kanseri nedeni ile tedavi edilen iki hasta grubu üzerinde karşılaştırmalı analizi içermektedir. 11 Nisan 2018-11 Mart 2020 tarihleri arasında tiroid kanseri nedeniyle tedavi edilen hastalar Grup 1'e, COVİD-19 salgını sırasında 11 Mart 2020-11 Şubat 2022 tarihleri arasında tiroid kanseri nedeniyle tedavi edilen hastalar ise Grup 2'ye alındı.
Bulgular: Grup 1'de 163(%58) hasta Grup 2'de 117 (%42) hasta vardı. Preop yapılan ince iğne aspirasyon biyopsi (İİAB) sonucu olası malign veya malign gelen hastalar Grup 2'de anlamlı şekilde daha fazlaydı (p=0.001). Postop patolojik tanılarına göre kıyaslama yapıldığında gruplar arasında anlamlı olarak fark vardı, kötü diferansiye tiroid kanseri Grup 2'de daha yoğun olarak görüldü (p=0.018). Patolojik tümör çapı Grup 2'de anlamlı olarak daha büyüktü (p=0.001).
Sonuç: Tiroid hastalıkları ve kanseri açısından şüpheli bulguları olan hastalar hem COVİD-19'a yakalanma korkusu nedeniyle hem de tüm dünya sağlık otoritelerince önerilen ve uygulanan pandemi tedbirleri neticesinde hastaneye daha geç başvuruda bulundu. Bu hastalar ilerleyen dönemlerde şikayetlerinin giderek artmasıyla hastaneye başvurdu, bununla paralel olarak tiroid kanseri tanısında gecikme yaşandı ve hastalık daha ileri bir safhada tespit edilebildi.

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Anahtar sözcükler: COVİD-19, tiroid kanseri, ameliyat

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Introduction

Thyroid cancers are the most common endocrine cancers. In the last 50 years, the incidence of thyroid cancer has increased more than 2 times all over the world due to the developments in diagnostic methods and the real numerical increase in the number of thyroid cancers [1]. Thyroid cancer is seen with a frequency of 2% in women and 0.5% in men among all malignancies [2]. Compared to other cancers, they are generally known as cancers that show well-differentiated histological features, have the best response to treatment, and offer a long life expectancy [3]. A new coronavirus, SARS-CoV-2, was first identified in patients presenting with symptoms such as fever, cough, weakness, and shortness of breath in December 2019, and this deadly disease was named COVID-19 [4,5]. The World Health Organization declared a global epidemic related to COVID-19 on March 11, 2020 [6]. The COVID-19 pandemic has seriously endangered the health of people around the world [7]. At the same time, serious effects emerged both physically and mentally in healthcare workers and patients working at an intense pace during the pandemic [8,9]. With the first cases to be seen in our country in March 2020, all health institutions were accepted as pandemic hospitals and it was recommended not to apply to health institutions when it is not necessary. The Ministry of Health decided to stop elective surgical procedures in hospitals on March 17, 2020, and with the pandemic measures taken in the following period, a significant decrease was observed in applications to hospitals and emergency services. Both the measures are taken and the fear of contracting COVID-19 affected patients' access to healthcare [10]. Although nearly 2 years have passed since then, the COVID-19 disease still continues to maintain its lethal effect with a fluctuating course and the development of different mutations. According to the data of the Ministry of Health in our country, as of February 24, 2022, the total number of cases due to COVID-19 was reported as approximately 14 million people and the total number of deaths was 93,000 people [11]. In all this process, even if patients have suspicious symptoms in terms of thyroid diseases and cancer, it is too late to apply to the hospital, and whether COVID-19 has affected the stage of thyroid cancer disease at the time of diagnosis. Our study, in patients diagnosed with thyroid cancer during the COVID-19 period; In this study, it was aimed to evaluate the effects of the pandemic measures recommended and implemented by all world health authorities and the fear of being infected with SARS-CoV-2 on the delay in diagnosis and the stages of the disease at the time of diagnosis.

Material and Methods

Our study was conducted retrospectively with the ethics approval of the Ministry of Health and the institutional review board (approval number: 2022/88, date: April 7, 2022).

The study includes a comparative analysis of patients diagnosed with thyroid cancer and treated in our clinic during the COVID-19 pandemic period, which started as of March 2020 and continues until today, and patients diagnosed with thyroid cancer treated in the same time period before the COVID-19 pandemic. The patients were divided into two groups. Patients who were treated for thyroid cancer between April 11,2018 and March 11,2020 were included in Group 1, and patients who were treated for thyroid cancer between March 11, 2020 and February 11,2022 during the COVID-19 epidemic were included in Group 2.

Patients' age, gender, number of nodules in preoperative ultrasonography (USG) and diameter of the suspicious nodule, Bethestda classification criteria in fine-needle aspiration biopsy (FNAB), histopathological diagnosis of surgical specimens, pathological tumour diameter, lymph node metastasis, postoperative complications and postoperative hospital stay Group It was recorded separately for Group 1 and Group 2. Differences between groups were compared. Although our study was retrospective, all patients were contacted from the phone numbers registered in the hospital system and it was questioned whether any complications occurred in the early or late postoperative period.

Patients who were operated on for benign reasons, whose postoperative pathology results were found to be benign, and patients who could not be reached by telephone were excluded from the study.

Statistical Analysis

Data IBM SPSS Statistics for Windows. Armonk, NY, USA, IBM Corp. analyzed with software. The numerical data obtained in the study are shown with mean and standard deviation values, and categorical data are shown with numbers and percentages.

Relationships between categorical data were evaluated using the chi-square test. The distribution characteristics of continuous data were determined with the Kolmogorov Smirnov test and the differences of numerical variables between the groups were evaluated with the Mann Whitney U test. In all statistical analyses, the level of significance was accepted as $p<0.05$.

Results

A total of 280 patients were included in the study. There were 163 (58%) patients in Group 1 and 117 (42%) patients in Group 2. Of the patients, 87 (31%) were male and 193 (69%) were female. There was no significant difference between the groups in terms of gender (p=0.380; Table 1). There was no significant difference in mean age in both groups (p=0.078; Table 1). The number of nodules and their diameters were checked in the USG, which was performed preoperatively. While the number of nodules was 2.64

(±1.56) in Group 1, it was 2.56 (±1.65) in Group 2. While the nodule diameter was 24.6 (±15.6) in Group 1, it was 22.6 (±16.8) in Group 2. In the preoperative USG evaluation, no difference was observed between the two groups in terms of nodule numbers and diameters (p=0.421, p=0.076, respectively; Table 1).

The patients were divided into two groups according to the results of the preoperative FNAB. Accordingly, Bethesda 1-2-3 was classified as benign and probable benign, and Bethesda 4- 5-6 as probable malignant and malignant. In group 1, FNAB was found to be benign and probable benign in 90 (55%) patients, while FNAB was found to be probable or malignant in 73 (45%) patients. In Group 2, FNAB was found to be benign and probable benign in 40 (34%) patients, while FNAB was found to be probable or malignant in 77 (66%) patients.

Patients who underwent preoperative FNAB and whose biopsy result was possibly malignant or malignant were significantly higher in Group 2 (p=0.001, Table 1).

Table 1. Demographic and preoperative data of the patients

	Group 1 (2018-2020)	Group 2 (2020-2022)	P
Number of patients, n (%)	163(58)	117(42)	
Gender, n (%)			
Male	54(33)	33(28)	0,380
Female	109(67)	84(72)	
Age*, year	49,54 (±11.39)	46.5 (±13.25)	0.078
Number of nodules*, n	2.64 (±1.56)	2.56 (±1.65)	0.421
Nodule diameter*, mm	24.6 (±15.6)	22.6 (±16.8)	0.076
Besthesda classification, n (%)			
Benign-possibly benign	90 (%55)	40 (%34)	**0.001**
Possible malign-malign	73 (%45)	77 (%66)	

*Data is presented as mean (standard deviation).

The patients were also compared according to their postoperative pathological diagnosis. Accordingly, papillary ca in 149 (91%) patients in Group 1, follicular ca in 11 (7%) patients, and medullary ca in 3 (2%) patients. In group 2, papillary ca in 92 (79%) patients, follicular ca in 17 (14%) patients, medullary ca in 7 (6%) patients, and anaplastic ca in 1 (1%) patient. There was a significant difference between the groups when compared according to their postoperative pathological diagnoses (p=0.018, Table2).

In the pathological examination, the macroscopic tumour diameter was 11.75 (±12.98) mm in Group 1, while it was 15.97 (±14.34) mm in Group 2. Pathological tumour diameter was significantly larger in Group 2 (p=0.001, Table 2).

Lymph node metastasis was present in 12 (7%) patients in Group 1, while it was observed in 17 (15%) patients in Group 2. Although lymph node metastasis was high in Group 2, there was no significant difference between the two groups (p=0.072, Table 2).

Postoperative complications occurred in 7 (4%) patients in Group 1 and in 12 (10%) patients in Group 2. Although postoperative complications were higher in Group 2, there was no significant difference between the groups (p=0.057, Table 2).

Table 2. Pathological characteristics and postoperative data

	Group 1 (2018-2020)	Group 2 (2020-2022)	P
Pathological diagnosis, n (%)			
Papillary thyroid cancer	149(%91.4)	92(%78.6)	
Follicular thyroid cancer	11(%6.7)	17(%14.5)	**0.018**
Medullary thyroid cancer	3(%1.8)	7(%6)	
Anaplastic thyroid cancer		1(%0.9)	
Tumor diameter*, mm	11.75 (±12.98)	15.97 (±14.34)	**0.001**
Lymph node metastasis,n(%)			
Yes	12(%7.4)	17(%14.5)	0.072
No	151(%92.6)	99(%85.5)	
Postoperative complications, n (%)			
Yes	7(%4.3)	12(%10.3)	0.057
No	156(%95.7)	105(%89.7)	
Length of stay*, day	2.85(±1.33)	3.40(±4.43)	0.459

*Data is presented as mean (standard deviation).

The hospitalization period of the patients was 2.85 (±1.33) days in Group 1 and 3.40 (±4.43) days in Group 2. There was no difference between the groups in terms of length of hospital stay (p=0.459, Table 2).

Discussion

COVID-19 has caused serious changes in the structure of health systems in our country and in the world. The pandemic has negatively affected humanity in many ways. Studies have been conducted on surgical procedures and precautions to be taken under emergency and elective conditions during the COVID-19 pandemic [12-15]. In addition, declarations recommend that elective surgeries should be stopped, only emergency patients should apply to hospitals, and that cancer surgery should continue [16,17]. People with suspicious findings in terms of thyroid cancer may have preferred to wait by delaying the application to the health institution due to the fear of contracting the disease and the additional measures applied in the health system. Accordingly, thyroid cancer patients may have applied at more advanced stages of the disease.

In our study, it was observed that the number of patients we operated on decreased significantly during the COVID-19 pandemic period (Table 1). This result suggested that patients with suspected compression symptoms such as neck pain, swelling in the neck, palpable stiffness, dysphagia, and hoarseness ignored this condition and delayed applying to the health institution. This result brings to mind two things: People did not apply to any health institution because they were afraid of catching diseases from the outside environment or hospitals, or they could not reach health services or were delayed in diagnosis due to changes in the health system such as stopping elective surgeries and limiting the number of polyclinic examinations during the pandemic period.

Exposure to ionizing radiation has been shown to be the only proven cause for the development of thyroid cancer [18]. On the other hand, the fact that the disease is more common in women than in men has led to the idea that female gender is a possible epidemiological risk factor [19]. In a study by Irribaren et al. reported that female gender is a relative risk factor for the development of thyroid cancer [20]. In our study, it was observed that the number of female patients was higher in both groups, but it was not statistically significant (p=0.380, Table 1). We think those sex hormones and other molecular factors are effective in this difference between the two sexes, since the disease is especially seen in women of reproductive age.

The female-to-male ratio in thyroid cancer incidence increases during adolescence and remains stable with advancing age. In their study, Farahati et al. reported that the ratio of females to males in childhood and adolescence is approximately 14 times [21]. In other studies, it has been shown that this rate is 3-5 times and decreases with advancing age [22,23]. Thyroid cancer is generally in grades 4-6. It is seen in decade [24,25]. In our study, the disease was mostly seen in the 4th and 5th decades in both groups, which was consistent with the literature, but no statistically significant difference was found between the two groups (p=0.078, Table 1). We think that exposure to environmental factors with advancing age has an effect on the development of thyroid cancer.

Thyroid nodules are very common, occurring in 20% to 76% of adults, and the incidence increases with age [26]. Although most of the thyroid nodules are benign, approximately 5% of them are at risk of malignancy [27]. It has been reported that approximately 4-7% of adults have a palpable thyroid nodule and the nodule diameter is smaller than 10 mm in approximately 70% of the nodules seen on USG [28]. The probability of thyroid cancer in a patient with a thyroid nodule larger than 10 mm in diameter is independent of the number of thyroid nodules [29]. In our study, no significant difference was observed between the two groups in terms of nodule number and nodule diameter (p=0.421; p=0.076, Table 1).

The Bethesda system was introduced in 2007 to standardize the terminology used in reporting thyroid cytology. There are six categories for thyroid cytology reporting in the Bethesda system, and each category is supported by a list of criteria [30]. The risk of malignancy for each category in the Bethesda system is variable. Category 1 1-4%, category 2 0-3%, category 3 5-15%, category 4 15-30%, category 5 60-75%, and category 6 97-99% [31]. In our study, we divided the patients into two groups according to the results of FNAB. Accordingly, we classified the patients admitted to Bethesda 1-2-3 as benign-probably benign, and the patients admitted to Bethesda 4-5-6 as probable malignant-malignant.

According to the grouping we made in our study, we found that the number of patients in the possible malignant-malignant group was significantly higher in the post-COVID-19 period (p=0.001, Table 1). Due to the restriction of the number of polyclinic examinations during the COVID-19 pandemic, the decrease in the number of patients admitted to hospitals, the fact that surgical procedures are performed very selectively, and perhaps our surgeons' desire to have less surgery due to the fear of contracting the COVID-19 disease, and also because of the late admission of patients due to fear, this is not the case. result may have occurred.

90% of thyroid cancers originate from the follicular epithelium, and these are well-differentiated papillary or follicular cancers [32]. Other than that, medullary thyroid cancer and anaplastic thyroid cancer are poorly differentiated cancers. Medullary thyroid cancer is seen with a frequency of 2-5% [33]. Anaplastic thyroid cancer is seen with a frequency of about 1% and is also considered the most aggressive type of thyroid cancer [34]. Studies have been conducted to examine whether COVID-19 predisposes patients to cancer, including thyroid cancer [35,36]. Whimbey et al. demonstrated in their

study that immune compromised cancer patients, including thyroid cancer, have an increased risk for community-acquired respiratory viruses [37]. The cause of the increased risk is multifactorial, including impaired cellular and humoral immunity, invasive vascular lines, and local tumour effects. It was observed that there was a significant difference between the two groups in patients with pathological diagnosis in our study. Accordingly, it was found that poorly differentiated thyroid cancer was more common in the post-COVID-19 period (p=0.018, Table 2). We think that the reason for this may be the changes that the virus makes in cellular and humoral immunity, microvascular changes and possible changes in cancer genetics, especially in people who have been infected with COVID-19.

Rostan et al. demonstrated in their study that there is a linear relationship between the increase in tumour diameter in thyroid cancer, and mortality and recurrence [38]. In addition, in our study on colorectal cancers during the COVID-19 period, it was found that the tumour diameter, lymph node metastasis, and stage of the disease advanced with the delay in diagnosis [39]. In our study, it was found that the tumour diameter was significantly larger in Group 2. Lymph node metastasis was also higher in Group 2, but it was not statistically significant (p=0.001, p=0.072; Table 2). We think that the reason for this is the effects of the restrictions applied during the pandemic period and the late admission of patients due to illness.

Today, thyroidectomy is an operation with low mortality and complications [40]. Complications of thyroidectomy can be divided into two groups as intraoperative and postoperative complications. The ability of complications to be prevented or reduced is related to the factors affecting it. The experience of the surgeon performing the operation, the characteristics of the patient and the disease are of great importance. In our study, more complications were experienced in Group 2, but it was not statistically significant (p=0.057, Table 2). The patients in Group 2 were patients with long-standing and advanced cancer. In our opinion, the fact that the surgery undergone by the patients was more complicated may have increased the postoperative complication rates.

In our study, when the mean hospital stay in the postoperative period was compared, no statistically significant difference was found between the two groups (p=0.459, Table 2). This study has several limitations. We may not have been able to accurately detect early postoperative complications, since most of the patients who underwent thyroidectomy were discharged within a few days. All patients were contacted by telephone and asked whether any complications occurred in the early or late postoperative period. However, patients who had surgery a long time ago may have given incorrect information.

Conclusion

Due to the COVID-19 pandemic, patients presenting later causes more complex patients and more advanced disease. This showed us that patients do not seek timely and appropriate care. It should be kept in mind that the increase in the stages of the disease with the delay may cause higher complication rates, increased morbidity and mortality, prolongation of hospitalization and increase in patient costs. We will need social awareness in order to address patient fears and to emphasize the right timing in hospital admissions in new pandemic diseases that may occur in the future. More research is needed so that we can be more organized about the course of thyroid cancer and patient management during epidemics.

Ethics Committee Approval: This study was conducted in accordance with the amended Declaration of Helsinki. The institutional review board (Decision No: 2022/88) approved the study, and all participants provided written informed consent.
Peer-review: Externally peer-reviewed.
Conflict of Interest: The authors have no conflicts of interest to declare.
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