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Thyroid fine needle aspiration biopsy results before and during the COVID-19 pandemic: From a single-center perspective

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Abstract

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Aim: One of the effects of the COVID-19 pandemic on the healthcare system has been the postponement of elective procedures. We aimed to investigate how the COVID-19 pandemic has affected our thyroid fine-needle aspiration biopsy (FNAB) results.

Materials and Methods: The distribution of cytology results during the 16.5 months of the pandemic was compared with the pre-pandemic period by The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) diagnostic categories.

Results: The number of FNABs performed during the pandemic period decreased by 27.3% compared to the pre-pandemic period in our center, in line with the recommendations (1,197 to 327 diagnostic FNABs). Benign biopsy results decreased during the pandemic period compared to the pre-pandemic period (77.3% to 49.5%, $p < 0.001$), and indeterminate biopsy results (AUS/FLUS, FN/SFN, and SUS) increased from 19.5% to 45.9%, $p < 0.001$. Malign biopsy rates did not differ between pre-pandemic and pandemic periods (3.3% to 4.6%, $p = 0.25$).

Conclusion: Although the number of FNAB decreased due to pandemic measures, we found a decrease in benign cytology and an increase in indeterminate for malignancy. The pandemic period allowed us to be more selective when deciding on a biopsy for FNABs. We recommend that the risk assessment of nodules be done carefully when making the biopsy decision in the next period. Although it is recommended not to delay FNAB for nodules at risk for malignancy, it should not be forgotten that the surgical decision should not be hasty in indeterminate results, and follow-up can be continued, or biopsy can be performed again under appropriate conditions.



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Introduction

Thyroid nodules are common and most of the nodules are benign [1]. As the malignancy rate is about 5-10%, it is important to distinguish between benign and malignant nodules in order to prevent unnecessary surgeries [2]. Ultrasound (US) has been widely used in the initial evaluation of thyroid nodules; however, it is not sufficient alone in the differentiation of benign and malignant nodules. Fine-needle aspiration biopsy (FNAB) is the best method to determine whether a nodule is benign or malignant [3-5]. At the end of 2019, a novel pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease-2019 (COVID-19) was reported in Wuhan, China. On March 11, 2020, the first SARS-CoV-2 case was reported in Turkey on the same day as

the COVID-19) pandemic declaration by the World Health Organization (WHO) [6]. The COVID-19 pandemic not only affected all areas of life but also caused significant changes in the healthcare system. Due to the rapid increase in the number of daily cases, pandemic prevention measures began to be implemented [7,8]. In addition, it was reported that handling of aspirated material could expose professional staff to potential COVID-19 transmission [9]. Therefore, in accordance with the international endocrinology guideline recommendations, elective FNAB procedures were postponed in our center due to the risk of transmission through close contact [7,8]. However, in the following few months, elective procedures were resumed as more information about SARS-CoV-2 infection and infection control was learned and it was thought that the pandemic would continue for a while. FNAB procedures were suspended on March 15, 2020 and started to be im-

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plemented again as of June 1, 2020.

This study aimed to evaluate how the COVID-19 pandemic has affected our thyroid FNAB results. We evaluated how the number of FNABs and the distribution of cytopathology results changed during the pandemic compared to before the pandemic according to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) diagnostic categories [10].

Materials and Methods

Data from patients who underwent FNAB at the Endocrinology and Metabolism center during both the pandemic and pre-pandemic period were retrospectively scanned. The sample size was determined according to the number of FNAB procedures performed in the same time period before and after the start of the pandemic, which was the first day. It was planned to include all cases from this probability sampling group with a stratified sampling system. FNAB results from the pandemic period (March 16, 2020 to July 30, 2021) and pre-pandemic period (November 1, 2018 to March 15, 2020) were evaluated separately. Those who had a previous history of thyroid cancer surgery, FNABs due to residual or recurrence and lymph node results were excluded from the study. Results of the diagnostic guide FNABs were analyzed according to the TBSRTC classification. Patients who underwent surgery and final pathology results were evaluated.

Cytopathology results were classified by TBSRTC into six categories (“non-diagnostic/unsatisfactory” [ND/UNS], “benign,” “atypia of undetermined significance/follicular lesion of undetermined significance” [AUS/FLUS], “follicular neoplasm/suspicious for a follicular neoplasm” [FN/SFN], “suspicious for malignancy” [SUS], and “malignant”) [6]. ND/UNS results were excluded from the study.

Diagnostic FNAB results were categorized into three groups: positive for malignancy, negative for malignancy, indeterminate for malignancy. Indeterminate results included AUS/FLUS, FN/SFN and SUS. The final histopathology of the patients who were referred to surgery due to the risk of malignancy was also evaluated.

All FNAB procedures were US-guided. Before the FNAB procedures, all patients were informed about the procedure and their written consent was obtained. FNAB was performed while the patient was placed supine and the neck was in extension. The skin was cleaned with alcohol and the nodule to be sampled was confirmed with US. The nodule was entered with a 22-gauge fine needle connected to a 10-mL syringe. Samples were taken with aspiration technique, by making one or more entrances until it was considered that the material was sufficient. The needle content was spread on a slide and then the smear was prepared by touching another empty slide to the surface of the first slide and separated again. Some slides were left to alcohol-dry and some samples were put in liquid-based cytology solution. All the samples were sent to the pathology laboratory.

During the Covid-19 pandemic period, indication of biopsy of a nodule was evaluated by at least two different endocrinologists in order to avoid unnecessary biopsies. A SARS-CoV-2 PCR test was requested from patients 48-72 hours

before the procedure day. Physicians and allied health personnel used personal protective equipment including FFP2 or FFP3 masks, protective glasses, disposable gowns and gloves. Because of the risk of contamination, at the beginning of the pandemic alcohol-drying method was not performed, only liquid-based cytology solution was used.

The primary endpoint of the study is the narrowing of indications due to the difficulty in performing biopsies due to pandemic conditions. The secondary endpoint is to assess the effect of decreasing FNABs during the pandemic period on cytology results. This study had two hypotheses. This study had two hypotheses. The first hypothesis was that the decreasing number of FNABs during the COVID period would not affect the overall rate of cytology results. The second hypothesis was that performing fewer FNABs would reduce the number of procedures on benign nodules without missing malignant ones. The difference between the groups for both hypotheses was examined with the Chi-Square test. Study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Local Ethics Committee of Gazi University Faculty of Medicine (Date: 2021/Protocol number: 171).

Statistical analysis

IBM SPSS Statistics 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, IBM Corp.) computer package program was used. Continuous variables were presented as the mean \pm standard deviation (SD). Chi-square (categorical variables) and student T tests (continuous variables) were used to assess differences between groups. $P < 0.05$ was considered to be statistically significant.

Results

Before the COVID-19 pandemic, 1,197 diagnostic FNAB were performed, and 327 diagnostic FNAB were performed during the pandemic. The mean age was 53.3 ± 12.8 and 51.1 ± 12.4 years before and during the pandemic, respectively, ($p < 0.001$). The vast majority of patients were women in both periods (79% before and 81% during the pandemic, $p > 0.05$). There was no significant difference between the sampled thyroid nodule size before and during the pandemic (19.8 ± 10.3 mm vs 20.7 ± 9.9 mm, $p > 0.05$). There was not statistically significant difference between TSH levels before and during the pandemic (1.8 ± 1.5 μ IU/mL vs 1.7 ± 1.6 μ IU/mL, $p > 0.05$). In our study, we observed that the number of benign FNAB decreased compared to the prepandemic period (77.3% to 49.5%, $p < 0.001$), and the number of indeterminate FNAB increased significantly (19.4% to 45.9%, $p < 0.001$). Although malignant cytology results increased from 3.3% to 4.6%, no statistically significant difference was found. A statistically significant difference was detected in the malignancy negative and indetermined results, shown in Table 1.

The histopathology results of the 125 patients who underwent surgery before the pandemic and 81 patients during the pandemic were also evaluated and compared with previous results of FNAB. When the surgical results of

Table 1. Characteristics of FNAB performed before and during the Covid-19 pandemic.

| | Pre-pandemic period | Pandemic period | P value |
|---------------------------------------|---------------------|-----------------|---------|
| Diagnostic FNAB (n) | 1197 953 (79) | 327 266 (81) | 0.4 |
| Women sex (n,%) | 53.3±12.8 | 51.1±12.4 | <0.001 |
| Age (years) | 19.8±10.3 | 20.7±9.9 | 0.2 |
| Nodule size (mm) TSH (µIU/ml) | 1.8±1.5 | 1.7±1.6 | 0.6 |
| Fine Needle aspiration biopsy results | | | |
| Negative for malignancy (n,%) | 925 (77.3) | 162 (49.5) | <0.001 |
| Indeterminate for malignancy | 233 (19.4) | 150 (45.9) | <0.001 |
| Positive for malignancy (n,%) | 39 (3.3) | 15 (4.6) | 0.2 |

FNAB: Fine needle aspiration biopsy; Negative for malignancy: benign FNAB results; Indeterminate for malignancy: AUS: Atypia of undetermined significance, FLUS: follicular lesion of undetermined significance, FN/SFN: Follicular neoplasm/Suspicious for a follicular neoplasm, SUS: Suspicious for malignancy FNAB results; Positive for malignancy: malignant FNAB results.

Table 2. Surgical outcomes of nodules pre-pandemic and pandemic periods.

| | Pre-pandemic period | | Pandemic period | | P value |
|------------------------------|---------------------|-----------|-----------------|-----------|---------|
| | Benign | Malignant | Benign | Malignant | |
| Indeterminate for malignancy | 39 (43.8) | 50 (56.2) | 44 (64.7) | 24 (35.3) | 0.009 |
| Positive for malignancy | 0 | 36 (100) | 0 | 14 (100) | |

indeterminate for malignancy FNAB were evaluated, the rate of malignancy in the pre-pandemic period was 56.2 %, whereas, it was 35.3 % in the pandemic period, this difference was found statistically significant (p=0.009). All FNAB positive for malignancy results in both periods were consistent with malignancy (Table 2).

Discussion

FNAB of thyroid nodules at risk of malignancy play an important role in excluding thyroid cancer. More rigorous evaluation of indications may help more satisfactory outcomes and avoid unnecessary surgical indications. With the declaration of the COVID-19 pandemic in March 2020, strict closure measures began to be implemented in many countries. Although the quarantine regime was not implemented in Turkey, precautionary measures began to be implemented with WHO recommendations.

With the COVID-19 pandemic becoming the focal point of our lives, many procedures in the health system needed to be reviewed. In the early days of the pandemic, FNAB were suspended and postponed in this context, as the procedure is an elective procedure. In addition, even if the nodule is malignant, since thyroid cancers usually progress slowly, it was thought that delaying these procedures would not have a negative effect for the prognosis [7]. The aim was to keep the patient group considered at risk for COVID-19, such as the elderly subjects or the patients with chronic diseases, away from the environments that would pose a risk of transmission to control the rate of infection spread.

In a study conducted by Palladino et al., it was reported that although FNAB numbers decreased significantly after the onset of the pandemic, the rates of SUS and malignant biopsies increased, and the rate of benign FNAB decreased [11]. In another study by Rossi et al., the results of FNAB

performed before the pandemic and during the pandemic period were evaluated, and it was seen that there was no statistically significant difference between the two periods according to the diagnostic categories, and the results of cytology and histology were compatible when the surgical pathologies of those with high-risk FNAB results were evaluated [9]. In our study, similar to the study of Palladino et al., although there was a significant decrease in the total number of FNAB, it was observed that the rates of benign FNAB decreased, and the rates of SUS and malignant FNAB increased. Our study also included a more extended period (evaluated 16.5 months of the pandemic), despite the time limitation in both studies (in both studies, eight months were evaluated, including the pre-pandemic period), which meant that FNAB applications continued with similar indications during the ongoing pandemic.

In our study, surgical outcomes of FNABs with indeterminate of malignancy and malignant were evaluated. It was determined that the rate of malignancy decreased in indeterminate cytologies during the pandemic period. We found that the rate of final malignancy decreased in indeterminate cytologies during the pandemic period. We thought that the reason for the increase in indeterminate FNAB results may be due to technical issues such as the use of excessive equipment (glasses, visors, etc.) during the procedures during the pandemic, and keeping the number of biopsy entries low in order to shorten the procedure time. At the same time, when cytology results were evaluated during the pandemic period, we thought that FNAB results might be due to the fact that more pathologists reported the results than before the pandemic (it is thought that factors such as the use of alternate working hours may also affect) Another factor for the increased indetermined biopsy results might be the effect of SARS-CoV2 infection on thyroid tissue. In previous studies, SARS-CoV2 infec-

tion caused direct or immune-mediated damage to thyroid tissue. This may trigger an underlying autoimmune disease and cause temporary or permanent damage to thyroid cells [12]. During the pandemic, cases of thyroiditis caused by SARS-CoV2 have been reported in the literature. These subacute forms of thyroiditis may present with obvious clinical symptoms as well as with subtle clinical manifestations. Although it has been shown that COVID-19 infection stimulates inflammatory-immune responses in the thyroid gland and extensive damage to the follicular epithelium and parafollicular cells has been described, there is as yet no evidence linking SARS-CoV-2 with tumorigenesis in the thyroid gland [13]. The exact status of COVID-19 infection and vaccination of the patients who underwent FNAB is not known, so we think that there may be some changes in the thyroid tissue and thyroid nodules because of previous COVID-19 infections and/or vaccinations, which may have caused an increase in the number of indeterminate FNAB [14,15].

In our study, COVID PCR was routinely requested before the procedure for the patients to be treated with FNAB during the pandemic, and the procedures of the patients whose PCR results were positive were postponed to 2-3 weeks at the earliest, as PCR negativity was observed again. However, the inability to record pre-procedure vaccination status and COVID-19 history can be a limitation of our study. This makes it difficult to predict the effect of infection on thyroid tissue with the increase in results associated with Indetermined FNAB results.

Conclusion

In conclusion, our study found that the number of FNABs decreased due to pandemic limitations, while the rates of benign cytology results decreased and indeterminate of malignancy cytology increased. This situation showed that FNAB indications were applied more strictly during the pandemic, similar to the literature data. Nevertheless, the rate of malignancy did not increase in final surgical results despite the increase in the number of indeterminate biopsies in our study, we can conclude that we should not be hasty in being referring the patient to surgery in order to prevent the increase in unnecessary surgery rates in this process. We think that the ultrasonographic features of the nodule and patient-related risk factors should be reviewed before making the surgical decision according to the cytology results, and the strategy of following reasonable patients for a while can be applied.

Although the changes caused by COVID-19 and thyroid tissue infection have been shown in the literature, there is no study showing that it changes the nodule structure. New studies are required for the changes made by SARS-CoV2 infection to the thyroid and nodule tissue.

As a result, in our study, we see that there is a shift in the direction of indeterminate FNAB in the FNAB rates made during the pandemic process. This suggests that changes due to COVID-19 may continue in the thyroid tissue, and this situation should be kept in mind in the evaluation of indeterminate cytology.

Conflicts of interest

The authors have no conflict of interest to declare.

Ethical approval

The study was approved by the Local Ethics Committee of Gazi University Faculty of Medicine (Date: 2021, Protocol number: 171).

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