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# Tumor/Nodule Size Ratio: A Possible Reason for False-Negative Thyroid Cytology

Nihal Seden Boyoğlu, Özgür Yiğit, Okan Övünç, Suat Bilici, Ahmet Volkan Sünter

University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Otorhinolaryngology - Head and Neck Surgery, İstanbul, Turkey

## ABSTRACT

**Introduction:** Fine-needle aspiration cytology is useful for the diagnosis and management of thyroid nodules. However, false negatives for malignancy may occur and affect treatment success. In this study, we investigated carcinoma size itself as another possible reason for false-negative results.

**Methods:** We retrospectively reviewed patient charts who had undergone total thyroidectomy and complementary thyroidectomy. A total of 613 cases were investigated. Patients who had a final histopathological diagnosis of thyroid carcinoma were included, and 138 cases were eligible for the study. Patients were categorized into three groups according to their fine-needle aspiration biopsy reports: Benign cytology and atypical cells of undetermined significance (group 1), cytology suspicious for a follicular/Hurthle cell neoplasm (group 2), and suspicious or positive for malignancy (group 3).

**Results:** Group 1 consisted of 55 patients with a mean tumor/nodule size ratio of 0.5236. Group 2 consisted of 21 patients with a mean tumor/nodule size ratio of 0.76. Group 3 consisted of 62 patients with a mean tumor/nodule size ratio of 0.848. There were no differences between the groups in terms of nodule size measured by ultrasonography ($p=0.209$), but the diameter of the carcinoma focus within the nodule was significantly smaller in false-negative cases ($p<0.001$). There were no statistically significant differences between the groups in terms of multicentricity ($p=0.197$).

**Conclusion:** The size of malignant tumors may be more important than nodule size in explaining false negativity.

**Keywords:** Fine-needle biopsy, thyroid nodule, thyroid carcinoma

## Introduction

Thyroid nodules are a common condition encountered by physicians from different specialties. During the period when imaging methods were not as widespread, thyroid nodule incidence was reported to be 5 to 10% (1-3). As ultrasound, computed tomography, and magnetic resonance imaging became more available, the prevalence of thyroid nodules increased to a now-estimated range of 20 to 60% depending on age, gender, and geographical location (4,5).

Fine needle aspiration biopsy (FNAB) is the most respected method for the management of thyroid nodules. However, false-negative FNABs are a major problem, as they may result in a missed diagnosis of cancer. The sensitivity of FNAB for carcinomas in thyroid nodules is between 80% and 94%. False-negative rates are reported in a range from 3.6 to 21% in different studies (6-8).

In some studies, authors suggest that false-negative FNABs are more common in large nodules due to both sampling inaccuracy and altered pretest probabilities (9-14), but there is still no consensus because the data of others show that nodule size is not associated with false negative biopsy rates (15-19).

A obstacle in evaluating false-negative biopsy rates is that most of the benign cytology nodules do not need surgery. Therefore, most benign biopsies are not checked in the final histological diagnosis (15).

In this study, we reviewed patients who had undergone total thyroidectomy or complementary thyroidectomy. The general indications for surgery were suspicious or malignant biopsies, repeated inadequate biopsies, massive goiters causing compressive symptoms, significant retrosternal extension, and selected cases of hyperthyroidism.

The present study detect false-negative cytology performed in our clinic and to investigated possible reasons for false negativity.

## Methods

Ethical approval was obtained from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethical Committee of the hospital (approval number 1557, date: 07.12.2018).

**Address for Correspondence:** Nihal Seden Boyoğlu MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Otorhinolaryngology - Head and Neck Surgery, İstanbul, Turkey
**Phone:** +90 532 333 51 15 **E-mail:** nihalseden@hotmail.com **ORCID ID:** orcid.org/0000-0003-0137-1535

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Patients who had undergone total thyroidectomy or complementary thyroidectomy in our clinic between 2010 and 2018 were reviewed. A total of 613 cases were analyzed, and those who had non-diagnostic cytologies, biopsies performed without ultrasonography, or biopsies performed at another hospital were excluded from the study. Of the remaining 400 patients, those who had a benign final histopathological diagnosis were also excluded. Patients with a carcinoma other than the biopsied nodule were noted. These cases of incidentally diagnosed carcinoma on histological examination of a non-biopsied nodule were classified on the basis of the FNAB report of the biopsied nodule. All FNAB are done under ultrasonography by a senior radiologist. All FNABs were performed using a 22-G needle on a 10 mL syringe with ultrasound guidance.

A total of 138 patients were included in the study. Each patient's carcinoma category, maximum carcinoma diameter, maximum biopsied nodule diameter, multicentricity, FNAB cytology diagnosis, age, and gender information were recorded.

Patients were categorized into three groups according to their FNAB reports: Benign cytology and atypical cells of undetermined significance (group 1), cytology that was suspicious for a follicular/Hurthle cell neoplasm (group 2), and cytology that was suspicious or positive for malignancy (group 3). FNAB results were considered false negative in all patients except those with suspicious or malignant cytology (group 3).

### Statistical Analysis

Statistical analysis was conducted using SPSS version 24. To compare the three groups, Kruskal-Wallis test was performed for quantitative variables and chi-square test was performed for the categorical data. Statistical significance was concluded when $p<0.05$.

This study was presented as a written poster at AAO-HNSF 2019 Annual Meeting & OTO Experience.

## Results

A total of 138 patients had a final histopathological diagnosis of thyroid carcinoma, of which 38 (27.5%) had a benign FNAB report, 21 (15.2%) had atypia of undetermined significance/follicular lesion of undetermined significance, 17 (12.3%) had a diagnosis of follicular neoplasia/suspicious for follicular neoplasia, 25 (18.1%) had a FNAB report of "suspicious for malignancy," and 37 (26.8%) had a malignant FNAB report.

The descriptive statistics of the patients are shown in Table 1. In group 1, there were 55 patients (10 male and 45 female) with a mean age of 48.82±11.65 years. The mean tumor size was 11.6 mm, the mean nodule size was 23.1 mm, and the mean tumor/nodule size ratio was 0.52. The cancer was multicentric in 22 patients (40%).

In group 2, there were 21 patients (10 male and 11 female) with a mean age of 46.38±12.38 years. The mean tumor size was 24.9 mm, the mean nodule size was 32.3 mm, and the mean tumor/nodule size ratio was 0.76. The cancer was multicentric in 11 patients (52%).

In group 3, there were 62 patients (22 male and 40 female) with a mean age of 51.44±14.00 years. The mean tumor size was 20.8 mm, the mean nodule size was 23.9 mm, and the mean tumor/nodule size ratio was 0.84. The cancer was multicentric in 35 patients (56%).

There were no differences between the groups in terms of nodule size measured by ultrasonography ($p=0.209$), but the diameter of the carcinoma focus within the nodule was significantly smaller in false-negative cases ($p<0.001$). There were no statistically significant differences between the groups in terms of multicentricity ($p=0.197$).

The distribution of carcinoma types is shown in Figure 1 and subtypes among groups are shown in Table 2.

According to the FNAB cytology results, the false-negative rate of the follicular variant subtype was significantly higher in all (micro + non-micro) papillary carcinoma cases ($p<0.001$).

We also noted that in 25 of the 66 patients with false-negative cytologies, FNAB was performed on the dominant nodule, but the carcinoma originated from another nodule.

## Discussion

Many surgeons and clinicians are working to identify additional indicators to predict malignancy and hence to provide accurate recommendations for or against surgery. While nodule size is prioritized in many studies, nodule diameter and actual carcinoma diameter were treated together with similar importance in this study, each of them affects the ratio of the nodule size and tumor size.

**Table 1. Descriptive statistics of the patients classified by groups**

| | Group 1 (n=55) | Group 2 (n=21) | Group 3 (n=62) | p-value |
|---|---|---|---|---|
| Male | 10 | 10 | 22 | 0.023* |
| Female | 45 | 11 | 40 | |
| Age (year) | 48.82±11.65 (17-71) | 46.38±12.38 (24-67) | 51.44±14.00 (18-83) | 0.196** |
| Carcinoma size (mm) | 11.60±14.15 (1-72) | 24.90±21.14 (2-70) | 20.85±18.69 (2-90) | <0.001** |
| Nodule size (mm) | 23.10±15.22 (7-85) | 32.30±21.54 (7-85) | 23.90±18.41 (2-90) | 0.204** |
| Tumor/nodule size ratio | 0.52±0.35 (0.03-1.0) | 0.76±0.34 (0.04-1.0) | 0.84±0.21 (0.15-1.0) | <0.001** |
| Multicentricity | 22 (40%) | 11 (52%) | 35 (56%) | 0.197** |

*: Chi-square test, **: Kruskal-Wallis test

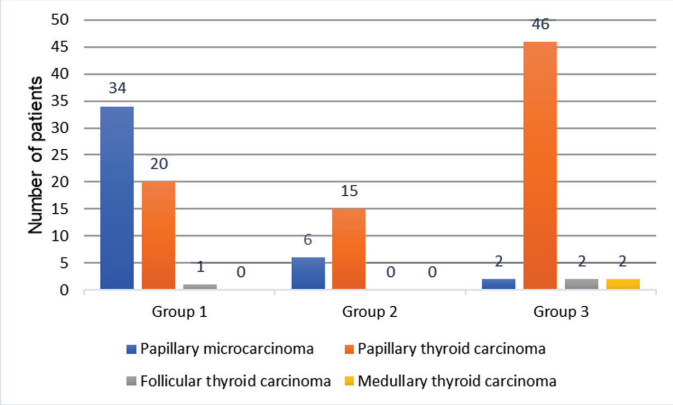


**Figure 1.** Carcinoma types among groups

**Table 2. Carcinoma subtypes among groups**

| Carcinoma type | Group 1 | Group 2 | Group 3 | Total |
|---|---|---|---|---|
| PMC-FV | 18 | 3 | 2 | 23 |
| PMC-CV | 11 | 2 | 9 | 22 |
| PMC-OV | 5 | 1 | 1 | 7 |
| PTC-FV | 10 | 12 | 12 | 34 |
| PTC-CV | 6 | 2 | 26 | 34 |
| PTC-OV | 4 | 1 | 8 | 13 |
| FTC | 1 | 0 | 2 | 3 |
| MTC | 0 | 0 | 2 | 2 |

PMC-FV: Papillary microcarcinoma-follicular variant, PMC-CV: Papillary microcarcinoma-classical variant, PMC-OV: Papillary microcarcinoma-other variants, PTC-FV: Papillary thyroid carcinoma-follicular variant, PTC-CV: Papillary thyroid carcinoma-classical variant, PTC-OV: Papillary thyroid carcinoma-other variants, FTC: Follicular thyroid carcinoma, MDC: Medullary thyroid carcinoma

Although the nodule diameter has been investigated for malignancy predictor, data from several studies are conflicting. Mehanna et al. (15) found that in nodules larger than 3 cm, the false-negative rate was 10.9%, and in nodules smaller than 3 cm, it was 6.1%; however, this was not statistically significant.

In some studies, false-negative rates were reported to be 17 to 19.3% in thyroid nodules of size 3 to 4 cm with benign preoperative cytology (10,11). McCoy et al. (11) were the first to investigate false-negative FNAB cytology rates of larger nodules. They reported that false-negative rates were markedly higher in nodules of 4 cm or larger than in smaller nodules.

In contrast, Porterfield et al. (16) found a false-negative rate of 0.7% for nodules larger than 4 cm. Additionally, Albuja-Cruz et al. (20) did not find any significant false-negative results in nodules larger than 4 cm. In another study, Shrestha et al. (21) went further and found that the smaller the nodule size (<1 cm), the greater the probability of false negativity. Of note, large thyroid nodules are more common in many surgical series because they are more likely to be operated on than smaller nodules due to problems such as compression symptoms.

In fact, the most common cause of false-negative FNABs reported in some studies is micropapillary cancer, which cannot be needle-aspirated in the same nodule as an adenomatous goiter (6,17). Some studies do not even consider cases with microcarcinoma as false negative (6,10,18,22,23). However, one area of broad agreement is that the vast majority of false-negative FNABs are micropapillary carcinomas (24-26). Concordantly, in this study, we found that the false-negative ratio was higher in micropapillary carcinomas and especially in follicular variants of papillary thyroid carcinomas.

Because of the combination of benign and malignant regions in the dominant nodule, false-negative results may occur due to cells in the remaining parts showing benign cytological features. Taking multiple aspirations from various parts of the nodule could decrease false-negative results arising from this heterogeneity.

Ylagan et al. (27) noted a 4% false-negative rate in 255 patients, most of whom had micropapillary carcinoma. They also found that false negativity was due to interpretation errors in 14 (6%) of the 255 cases, which was explained by the emergence of overlapping cytological features in adenomatous nodules, follicular neoplasms, papillary thyroid carcinoma follicular variants, and Hashimoto thyroiditis (27). Mehanna et al. (15) also found that the probability of having a false-negative biopsy from a follicular variant papillary carcinoma was significantly higher than that of conventional or other papillary carcinoma variants, which is in line with the results of the study by Albuja-Cruz et al. (20) and our study (10).

In this study, we also noticed that 37.8% of the false-negative biopsies were biopsy taken from a different nodule other than the nodule the tumor was in. This supports the need to perform biopsies of all nodules and not only of the dominant nodule.

A obstacle in evaluating false-negative FNAB rates in thyroid nodules is that most nodules with benign cytology are not operated on. Therefore, the final histolopathological diagnosis is unknown, in most cases.

In this study, there was no difference between the groups in terms of nodule sizes, we found that the tumor diameter was much smaller in the false negative group. This resulted in a statistically significant difference in tumor size/nodule size ratio. We couldn't suggest a cut-off value because it seems that the reason for this ratio was the difference in the size of the cancer foci.

To date, researchers have focused mostly on nodule size because it is the most accurate data available to guide the decision-making process. However, our study is novel because it focuses on the tumor/nodule size ratio, which is a different perspective.

### Study Limitations

This study has several limitations because we compared the results of FNAB with the postoperative pathology report. In other words, we only included patients who had undergone both thyroid nodule biopsy and surgery, and so patients who did not undergo surgery were excluded from the study. This was not a specificity-sensitivity study because we only evaluated carcinoma cases.

In this study, we could not suggest any information that could be useful in decision-making before thyroid surgery, but we have provided a different point-of-view regarding false-negative cytologies.

## Conclusion

The size of malignant tumors may be more important than the nodule size in explaining the false negativity of FNAB. The smaller the tumor size, the higher the false negative rate.

**Ethics Committee Approval:** Ethical approval was obtained from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethical Committee of the hospital (approval number: 1557, date: 07.12.2018).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

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