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## Comparison of the Results of Thyroidectomy and Second Fine-Needle Aspiration Biopsy of the Old Age Group with the Previous Bethesda III group: Is the second Biopsy necessary?

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### ABSTRACT

**Objective:** We aimed to detect if there were any radiologic, demographic, or clinical findings that were valuable for differentiating benign nodules from malignant nodules in old aged patients, when the results of the first fine-needle aspiration biopsy (FNAB) were reported as atypia of undetermined significance (AUS).

**Materials and Methods:** Patients aged 65 years and older who were biopsied from thyroid nodules were analyzed retrospectively in this study. A total of 1264 patients with 1374 nodules were enrolled and of these, 203 patients with 216 nodules were recorded to have diagnosis of AUS in pathological evaluation. We excluded 104 nodules on which FNAB had been performed only once and included 112 nodules, on which FNAB had been performed twice. Out of these included patients, a total of 43 patients were thyroidectomized. Preoperative ultrasonographic nodular findings, echogenicity, marginal [ir]regularity, calcification, exophytic configuration, and halo were recorded.

**Results:** The median patient age was 69 years. There was no statistically significant difference between the results of the first and second FNABs. Hypoechoogenicity was the only statistically significant different characteristic found in thyroid nodules that could effectively discriminate between malignant and benign groups.

**Conclusion:** The second FNAB does not increase the likelihood of diagnosing malignancy in old aged patients and there is no need for this procedure when recommending surgery. Suspicious USG findings are more frequent among malignant nodules, as reported in the histopathological evaluation of the old aged patients. A multidisciplinary team should take part in the decision-making process for the treatment of old aged patients after the first FNAB, with due consideration of the history, physical examination, USG, FNAB laboratory findings, and patient preference.

**Keywords:** Old age, FNAB, atypia of undetermined significance, thyroidectomy

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### INTRODUCTION

The frequency of thyroid gland disease increases with age. Multinodular goiter (MNG), affecting more than 300 million patients, is the most common thyroid disease worldwide (1). The occurrence rate of thyroid nodules also increases with age, predominantly in women (2). There are reports of up to 100% nodule identification in an autopsy series. The prevalence of goiter is reported to be 75% in patients ≥55 years of age and nodular goiter is 25% in this age group (3).

Thyroid nodules are discovered either incidentally or on physical examination. The main clinical question related to the nodules is whether they have potential to become malignant. History, physical examination, and imaging may give clues about the malignancy potential. Patients with head and neck radiation history, family history of thyroid cancer, rapid growth of neck mass, presence of a fixed mass, obstructive symptoms, cervical lymphadenopathy, or vocal cord paralysis in the physical examination have a higher risk for malignancy. There is growing evidence on the effectiveness of selecting nodules for fine-needle aspiration biopsy (FNAB) according to the suspicious characteristics identified on diagnostic imaging rather than the nodule size alone. Subcapsular location, extrathyroidal extension, extrusion through rim calcifications, abnormal cervical lymphadenopathy, irregular margins, incomplete halo, taller than wider shape, hypoechoogenicity of the nodule, and documented enlargement of the nodule are indications for FNAB and an increased risk of malignancy (4–6).

Although old-aged patients are reported to have increased rates of nodule frequency, they are also reported to show a decreased rate of malignancy but with more aggressive subtypes. In spite of these differences, there is no universally accepted approach towards the treatment of thyroid nodules in the geriatric population.

In this study, the same criteria as above were accepted as indications for FNAB in the old age group. The Bethesda system was used to report the results of the FNABs. This system has six categories to determine malignancy risk of a thyroid nodule: Category I [nondiagnostic (ND)], Category II (benign), Category III (atypia of undetermined

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significance/follicular lesions of undetermined significance (AUS/FLUS)) (7), Category IV (suspicious for follicular neoplasm (FN/SFN)), Category V (suspicious for malignancy (SFM)), and Category VI (malignant). Surgical treatment is indicated for categories IV–VI, clinical follow up for II and repeat FNAB for I and III. AUS/FLUS has a 5–15% risk of malignancy (8–10).

Repeated FNABs are frequently performed in clinical practice but this approach also increases patient anxiety, FNAB-related complications, and costs of treatment, and results in a delayed diagnosis. Although Cibas et al. showed malignancy rates of 5–15 % in patients with FNAB results of AUS/FLUS, current guidelines and recent studies recommend a repeat FNAB, molecular testing, follow-up, lobectomy, or core needle biopsy (11). Although aggressive subtypes of thyroid cancer are common in the old age group, there is less evidence on the standard approach for this age group for the patients who receive a result of AUS/FLUS from the second FNAB as well.

In this study, we aimed to determine the significance of repeated FNAB and ultrasonography (US) to estimate the malignancy rate in AUS/FLUS nodules in old aged patients.

## MATERIALS and METHODS

Patients with at least one AUS/FLUS nodule that was treated between January 2016 and December 2018 at Yildirim Beyazıt University Hospital were reviewed. We biopsied 23,587 nodules, of which 1,288 exhibited AUS/FLUS cytology. A total of 216 AUS/FLUS nodules were detected in patients  $\geq 65$  years of age and were included in this study. We excluded patients who presented with cytological results other than AUS/FLUS and patients who were younger than  $< 65$  years. Some nodules were biopsied only once, but others were biopsied twice to refine the diagnoses. Of these nodules, 104 nodules were biopsied once and 112 nodules were biopsied twice, while 43 underwent surgery. We compared AUS/FLUS nodules for malignancy rate according to the number of biopsies (once, twice) performed and also examined the role of ultrasonographic features in differentiating malignant from benign pathology. The Institutional Ethical Committee approved this retrospective study on 4/7/2019 (approval number: E-19-015). The Bethesda System was used for cytological evaluation. All the patients underwent thyroid US in our hospital and were recommended either for surgery on suspicion of malignancy or for a repeat FNAB or other follow-up, at the discretion of the attending thyroid surgeon/endocrinologist and considering the patient's preference. If the second FNAB showed AUS/FLUS nodules and revealed an ND, FN/SFN, SFM, or malignant status, surgery was recommended. If the second FNAB of an AUS/FLUS nodule showed an AUS/FLUS status again, the option of surgery was offered. In addition, some patients were operated upon to treat suspicious nodules (other than the index AUS/FLUS nodule) in the thyroid parenchyma. Additional operative criteria included a large multinodular goiter, sonographic features that were of concern (12), actively growing nodules, clinical suspicion, or patient/physician preference. Despite the suggestion of surgery, some patients requested a re-biopsy or other follow-up, and another section of patients were lost during the follow-up.

The demographic characteristics and thyroid autoantibody status were recorded. Thyroid peroxidase antibody (anti-TPO) and thy-

**Table 1.** Cytological results of second FNABs

	n	%
Nondiagnostic	47	42
Benign	39	34.8
AUS/FLUS	26	23.2
FN/SFN	0	0
SFM	0	0
Malignant	0	0
Total		112

n: Number; AUS/FLUS: Atypia of undetermined significance/follicular lesions of undetermined significance; FN/SFN: Suspicious for follicular neoplasm; SFM: Suspicious for malignancy

roglobulin antibody (anti-Tg) levels were measured via electrochemiluminescence immunoassay; the average values were  $< 5.61$  IU/mL and  $< 4.11$  IU/mL, respectively. Levels higher than average were considered positive and all other levels were considered negative. Esaote Colour Doppler US (Model 796FDII) using a superficial probe (Model LA523) was used for imaging. Preoperative US nodular findings, echogenicity, marginal [ir]regularity, micro- and macro-calcification status, and halo status were recorded. FNAB was performed using a 27-gauge needle and a 20 mL syringe under US guidance. The histopathological examination of nodules that underwent surgery revealed them to be either benign or malignant.

## STATISTICAL ANALYSES

All statistical analyses were performed using the IBM Statistical Package for Social Sciences for Windows ver. 23.0 (SPSS, IBM Corp, Armonk, NY, U.S.A). Fisher's exact test was used to evaluate the statistical significance of categorical variables. All p-values were two-sided, and  $p < 0.05$  was considered statistically significant.

## RESULTS

The median age of the patients was 69 (65–86 years) years. Female patients comprised 70.9% of the population study group. Anti-TPO was positive in 31.4% of patients and Anti-Tg was positive in 22.2% of patients.

The results of 47 (42%) second FNABs were non-diagnostic, 39 (34.8%) were benign, 26 (23.2%) were AUS/FLUS, while none (0%) were FN/SFN, SFM, or malignant. Cytological results of second FNABs are shown in Table 1.

A total of 43 (19.9%) of nodules underwent surgery. Of these, 32 (74.4%) were benign and 11 (25.6%) were malignant on histopathology. Fourteen (73.7%) nodules with once FNAB were benign on histopathology while 5 (26.3%) of them were malignant on histopathology. Eighteen (75%) nodules with twice FNAB were benign on histopathology while 6 (25%) were malignant on histopathology. The malignancy risk was similar in AUS/FLUS nodules with once or twice FNAB ( $p=1$ ). The histopathology results of AUS/FLUS nodules according to FNAB counts are shown in Table 2.

**Table 2.** Histopathology results of AUS/FLUS nodules according to FNAB counts

	once FNAB		twice FNAB		Total		p
	n	%	n	%	n	%	
Benign	14	73.7	18	75	32	74.4	
Malignant	5	26.3	6	25	11	25.6	1.0
Total	19		24		43		

FNAB: Fine-needle aspiration biopsy

Ultrasonography (USG) findings and anti TPO/anti-Tg positivity were compared according to histopathology results (Table 3). Hypoechoogenicity was higher in malignant nodules than in benign ones ( $p=0.04$ ). Absence of a halo, macrocalcification, microcalcification, irregular margins, anti-TPO positivity, and anti-Tg positivity were similar in benign and malignant nodules ( $p=0.41$ ,  $0.29$ ,  $1.0$ ,  $1.0$ ,  $0.23$ , and  $0.68$  respectively).

## DISCUSSION

In the Bethesda system, a result of AUS/FLUS is inconclusive, neither benign nor malignant, therefore, a follow-up, repeat FNAB, or thyroidectomy are all possible options for a clinical approach. Although FNAB is the gold standard for the diagnosis of thyroid cancer, nearly 10% of biopsies are reported as Bethesda I and 12% of biopsies are reported as Bethesda III, which means 1/4th of the biopsies are inconclusive (8). Furthermore, there are different rates of malignancy reported in different centers regarding the three categories of Bethesda (13, 14). Dincer et al. reported that this might be secondary to the FNAB technique, needle size, USG guidance use, or smear preparation technique (dry or alcohol-based), since inappropriate specimen preparation may lead to nuclear enlargement and irregular membrane formation (15).

According to our results, we conclude that in old age group, a repeat FNAB is unnecessary in patients with a previous AUS/FLUS cytology who are recommended for surgery (Table 2). Second FNAB is also not mandatory for taking a decision to perform thyroidectomy in this age group if the patient has been decided as a candidate for surgery based on the clinical evaluation with previous history, physical examination, imaging, laboratory evaluation, and patient preference. Our results support the findings of the studies suggesting that repeat biopsy does not affect the malignancy rate (16).

Absence of a halo, macrocalcifications, irregular margins, microcalcification, and hypoechoogenicity of the thyroid nodules are all features that are helpful in differentiating between malignant and benign nodules (17–19). In our study, only the presence of hypoechoogenicity was significantly higher in patients with malignant histopathology (Table 3). Similar to our results, Paini et al. reported that hypoechoogenicity with accompanying malignant features on a thyroid USG identifies lesions that should undergo cytologic examination (20). Further studies are needed before conclusive evidence can be reached that hypoechoogenicity may be the most sensitive or specific feature in USG for the accurate discrimination of benign from malignant thyroid nodules in the old age group.

**Table 3.** Comparison of ultrasonographic features and Anti TPO/Anti-Tg positivity of the nodules according to histopathology results

	Benign		Malignant		p
	n	%	n	%	
Absence of a halo	23	79.3	7	63.6	0.41
Macrocalcification	5	17.2	0	0	0.29
Hypoechoogenicity	5	17.9	6	54.5	<b>0.04</b>
Microcalcification	1	3.4	0	0	1.0
Irregular margins	1	3.4	0	0	1.0
Anti TPO positivity	6	24	5	50	0.23
Anti Tg positivity	5	20	3	27.3	0.68

TPO: Thyroid peroxidase

Thyroid nodules are detected in up to 76% of the adult population by USG and up to 100% during autopsy series (21, 22). The thyroid nodule burden is increasing worldwide, the frequency is known to increase with age, the world's population is aging, imaging modalities are utilized more frequently and are more sensitive (23). Keeping these factors in mind, it is critical that once a thyroid nodule is detected, appropriate management should be performed. This is also true for the old age group, i.e., after excluding thyroid functional abnormalities, thyroid nodules should be evaluated in terms of malignancy.

At this point, FNAB, although very helpful, is not always diagnostic. Thus, the clinician needs to weigh the benefits and risks of further evaluation versus a clinical follow-up. FNAB, although simple, reliable, inexpensive and safe, also has mild and rare complications like cutaneous sinus formation pain, hemorrhage/hematomas, recurrent laryngeal nerve palsy, needle track seeding of papillary carcinoma, nodule volume alteration, and thyrotoxicosis after aspiration (24, 25). Similarly, thyroidectomy also has complications, including hypocalcemia, hoarseness, dysphagia, wound infection, and death (26). In this study, we analyzed thyroid nodules of the old age group where there is diagnostic uncertainty after FNAB. Although it has been reported that there is a low likelihood of malignancy of thyroid nodules in old aged patients, these cancers have a more aggressive phenotype (27). Guidelines of endocrine and/or oncology societies frequently incorporate age into clinical staging systems, such as the American Joint Committee on Cancer, AGES (age, grade, extent, size), and MACIS (metastasis, age, completeness of resection, invasion, size) (23, 28). Although advanced age itself is not a risk for operative complications, surgeons also feel uncomfortable when operating upon a patient of advanced age, since age-related system changes and comorbid conditions may increase the perioperative and postoperative complication risk (29). Recently, Lillian Min et al. reported that age was not associated with any postsurgical complications, rather, the functional status determined by the Lawton and Katz scales and the self-assessed inability to manage alone after discharge were the leading risk factors for surgical outcomes. They also proved that postoperative sarcopenia is a relatively frequent occurrence (30).

In this retrospective study, we could not record the complication rates of FNAB or thyroidectomy, but we retrospectively reviewed

the mortality rates after thyroidectomy and FNAB from hospital records and a national database using citizenship numbers, after which we did not find any deaths that could be related to procedural or surgical complications directly. Therefore, we can conclude that the surgery is safe, at least in terms of the mortality rates of this age group.

In our study, we detected that hypoechogenicity is a significant determinant of malignancy in AUS/FLUS nodules. Second biopsy of AUS/FLUS nodules does not enhance the identification of the risk of malignancy.

Our work had several limitations. The number of patients who underwent the surgery was low. The study was retrospective in nature and the surgical decision-making (excision or repeat biopsy) was often influenced significantly by patient preference rather than the recommendations of surgeons or endocrinologists. Thus, it was difficult to derive a true malignancy rate. Moreover, most patients with category III cytology were advised to accept the follow-up without operation. Malignancy rates of only-operated patients may be associated with patient selection bias. The strong aspect of this study was that it is among the limited studies on thyroid nodule follow-up in the geriatric age group and the data have been collected from our own country.

## CONCLUSION

The second biopsy of AUS/FLUS nodules does not enhance the identification of the malignancy risk in patients in old age group. There is no need for a repeat biopsy of AUS/FLUS nodules to suggest surgery or follow-up for old aged patients. It should be noted that the hypoechogenicity seen in the ultrasound may be a predictor of malignancy.

**Ethics Committee Approval:** The Institutional Ethical Committee approved this retrospective study on 4/7/2019 (approval number: E-19-015).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

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

**Author Contributions:** Both of the authors contributed in concept, design, supervision, resource, materials, data collection and/or processing, analysis and/or interpretation, literature search, writing and critical reviews of the article.

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