Research Article

Evaluating Postoperative Outcomes and Investigating the Usefulness of EU-TIRADS Scoring in Managing Pediatric Thyroid Nodules Bethesda 3 and 4

Postoperative Outcomes and EU-TIRADS Scoring in Pediatric Thyroid Nodules

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What is already known on this topic?
The European Thyroid Imaging Reporting and Data System (EU-TIRADS), which is a risk stratification system utilized to evaluate the probability of malignancy in thyroid nodules based on ultrasound characteristics. This scoring system assists clinicians in determining whether to suggest biopsy or further monitoring of thyroid nodules. The EU-TIRADS scoring system has undergone comprehensive investigation in adult populations, demonstrating acceptable accuracy in the prediction of malignancy. The EU-TIRADS scoring system has the potential to be a useful tool for evaluating thyroid nodules in children, but its accuracy and effectiveness still require confirmation.

What does this study add?
This study represents the first comprehensive investigation in literature that assesses the postoperative outcomes and explores the utility of EU-TIRADS scoring in the management of pediatric thyroid nodules categorized as Bethesda 3 and 4 Postoperative pathologies revealed varying EU-TIRADS scores. EU-TIRADS 5 showed a lower percentage in cases with malignancy in Bethesda 3 cases compared to the low risk and benign group, while in Bethesda 4 cases, EU-TIRADS scores increased as postoperative pathology worsened. These findings underline the controversial results of the EU-TIRADS scoring system in guiding clinical decision-making for pediatric thyroid nodules.

ABSTRACT
Purpose: The study aimed to assess the postoperative outcomes of pediatric thyroid nodules with Atypia of Undetermined Significance (AUS/FLUS) or Suspicious for a Follicular Neoplasm (SFN) and their EU-TIRADS scoring
Methods: The study retrospectively reviewed 44 patients at a single center with thyroid nodules classified as Atypia of Undetermined Significance or Suspicious for a Follicular Neoplasm from August 2019 to December 2022. Data on demographics, thyroid function, nodule size, and ultrasonographic features were collected. Postoperative pathologies were categorized into benign, low-risk, and malignant neoplasms according to WHO 2022 criteria, with EU-TIRADS used for radiologic scoring.
Results: Among 21 pediatric patients, 72% had Bethesda 3 and 28% had Bethesda 4 thyroid nodules. Pathological outcomes post-surgery classified 43% as benign, 19% as low-risk, and 38% as malignant. Notably, EU-TIRADS 3 and 5 scores were present in 44% and 56% of benign cases, respectively. Malignant cases showed a prevalence of higher EU-TIRADS scores, with 64% rated as EU-TIRADS 5. Bethesda category 4 nodules had a 66% malignancy rate, significantly higher than the 27% in category 3.
Conclusion: The investigation revealed that EU-TIRADS scoring showed a substantial proportion of benign cases were classified as EU-TIRADS 5, suggesting that EU-TIRADS may lead to unnecessary biopsies in benign cases. Malignant cases were more likely to have a higher EU-TIRADS score, indicating a positive correlation with malignancy risk, particularly in Bethesda 4 cases. However, the EU-TIRADS system's predictive value for malignancy in Bethesda 3 cases was less definitive.

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2023-08-23
2024-01-13

1.   INTRODUCTION

Fine-needle aspiration (FNA) is a valuable method for guiding the therapeutic management of patients with thyroid nodules by estimating the risk of malignancy (1,2). The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) includes six diagnostic categories: I) non-diagnostic or unsatisfactory; II) benign; III) atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS); IV) follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN); V) suspicious for malignancy; and VI) malignant (1,3).

In childhood, Bethesda categories 3 and 4 are the two histopathologic diagnoses that clinicians have difficulty in deciding surgical decisions and risk of malignancy.

The malignancy risk for Bethesda category 3 and 4 is higher in children compared to adults(4). For Bethesda category 4 nodules, the risk of malignancy is greater than for category 3 nodules (5). The 2015 American Thyroid Association (ATA) 2015 guidelines recommend surgery for thyroid nodules classified as AUS/FLUS or FN/SFN on the first fine needle aspiration biopsy (FNAB) in order to definitively establish the diagnosis and provide appropriate treatment if the nodule is malignant (2). The 2022 ETA pediatric guidelines recommend repeating FNAB after six months for AUS/FLUS and FN/SFN nodules detected on the first FNAB. Surgical management is reserved for cases with significant growth, suspicious ultrasound (USG) features, or persistent cytological abnormalities. (6). The guidelines note that the risk of malignancy is higher in pediatric thyroid nodules compared to adult nodules, and that surgical management may carry greater risks and consequences in children due to their smaller size and less-developed anatomy. However, the guidelines do acknowledge that careful observation with repeat FNAB at 6 to 12 months may be an option in select cases, such as those with small nodules or those with significant comorbidities that increase the risk of surgery (2).

Bethesda category 3 and category 4 are both considered indeterminate categories, meaning that the risk of malignancy is unclear based on cytology alone. Therefore, additional evaluation and clinical correlation are needed to determine the appropriate management. It is important for clinicians to consider the individual patient's clinical and imaging features, as well as the specific histopathological diagnosis, when deciding on management for Bethesda category 3 and 4 nodules in children. TIRADS, which stands for Thyroid Imaging Reporting and Data System, is a set of risk stratification systems to categorize thyroid nodules based on ultrasound features (7,8). The term TIRADS can refer to multiple guidelines, including ACR-TIRADS (American College of Radiology) (9), EU-TIRADS (European Thyroid Association) (10), and K-TIRADS (Korean Society of Thyroid Radiology) (11,12). The EU-TIRADS is considered to have a more straightforward and possibly less time-consuming approach to nodule classification.The system, in which the high specificity US malignancy features include marked hypo-echogenicity, irregular shape, irregular margins, microcalcifications (10). While the EU-TIRADS scoring system has been extensively studied in adult patients and has shown good accuracy in predicting malignancy(13), there needs to be more data on its usefulness in childhood thyroid nodules. Some studies suggest that the EU-TIRADS scoring system may be helpful in childhood thyroid nodules(14), but further research is needed to confirm its accuracy and usefulness in this population.

In our study, we aimed to evaluate the postoperative outcomes of cases with AUS/FLUS and SFN detected in thyroid nodules and investigate their EU-TIRADS scoring.

2.   SUBJECTS AND METHODS

The study was conducted as a single-center retrospective cross-sectional analysis. It encompassed patients who presented with atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) and suspicious for a follicular neoplasm (SFN) on thyroid fine-needle aspiration biopsy (FNAB) between August 2019 and December 2022. According to the follow-up principle of thyroid nodules of our multidisciplinary team (pediatric endocrinologists, pediatric surgeons, pediatric radiologists, pediatric oncologists and pathologists), patients with thyroid nodules who are diagnosed as Bethesda category 3 in their initial biopsy and who do not show pathognomonic malignancy findings such as microcalcification, central vascularity or irregular borders on ultrasonographic evaluation are kept under observation. These cases were re-evaluated with ultrasonography after 3-6 months, followed by a second FNAB. Our study included 21 of the 44 patients who underwent surgical

intervention after being diagnosed with Bethesda categories 3 (AUS/FLUS) and 4 (FN/SFN) on FNAB of the thyroid. Of the remaining patients, ten were lost to follow-up, the second biopsies of six patients were interpreted as benign, and the seven patients had not yet reached the time for their post-biopsy follow-up. Demographic and clinical data such as age, gender, serum thyroxine (sT4), thyroid-stimulating hormone (TSH) levels, dimensions of thyroid nodules, sonographic characteristics, and histopathological findings post-thyroidectomy were saved from the institutional electronic medical records. The Bethesda System for Reporting Thyroid Cytopathology was employed to categorize the cytopathological findings of the thyroid fine-needle aspiration biopsies. The inclusion criteria encompassed cases classified as atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) under Category 3, as well as those specified as suspicious for a follicular neoplasm (SFN) under Category 4. It is noteworthy that our cohort did not consist of any patients classified as follicular neoplasm (FN). All participants underwent a complete thyroidectomy as part of their treatment protocol.

Post-operative pathology results were divided into three categories, as classified by the WHO in 2022: benign neoplasms, low-risk neoplasms, and malignant neoplasms. Low-risk neoplasms are non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), thyroid tumors of uncertain malignant potential (UMP), and hyalinized trabecular tumor (HTT)(15,16). In our study, we had cases with NIFTP and UMP. Radiologic features of the nodule were scored according to EU-TIRADS scoring system (2017) (10) The study was performed in accordance with the Helsinki Declaration of 1975. This study was approved by the Ethics Committee of Ankara City Hospital (Approval number/date) E2-23-3317/01.02.2023).

All data analyzes were performed with SPSS 26.0. Descriptive statistics were used to evaluate demographic and clinical characteristics. Data were defined as percent, mean ± standard deviation (SD), and median (minimum-maximum). The Chi-Square test was used for comparing categorical variables. While the investigating the associations between non-normally distributed and/ordinal variables, the correlation coefficients and their significance were calculated using the "Spearman test". Statistically, $p<0.05$ was considered significant.

3. RESULTS

In this study, 21 patients who underwent surgical intervention following a diagnosis of Bethesda categories 3 (AUS-FLUS) and 4 (SFN) on fine-needle aspiration biopsy (FNAB) of the thyroid were included. The median age of the participants was 15.4 years, with an interquartile range of 11 to 17.5 years. Females constituted 86% (n=18) of the patient population, while males represented 14% (n=3). A familial history of thyroid carcinoma was noted in one individual. Additionally, one patient was under surveillance for an ovarian neoplasm. Thyroid function tests revealed hypothyroidism in 5% (one patient), subclinical hypothyroidism in 10% (two patients), and euthyroid status in the majority, 85% (eighteen patients). Notably, 42% (n=9) of the patients presented with multiple thyroid nodules. Within this subgroup, 88% (eight patients) exhibited dual nodular formations, whereas a single patient (12%) had three nodules.

The postoperative pathological analysis indicated that 43% (n=9) were classified as benign, 19% (n=4) as low-risk neoplasms, and 38% (n=8) as malignant. Within the low-risk neoplasm category, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) constituted 75% (n=3) of the cases, while uncertain malignant potential (UMP) was observed in 25% (n=1) of the cases. Fine needle aspiration biopsy (FNAB) cytopathological results and the World Health Organization (WHO) classification of postoperative pathology are depicted in Figure 1.

On evaluating the postoperative outcomes of thyroid nodules in relation to their EU-TIRADS scores, we observed that in benign cases, 44% were rated as EU-TIRADS 3 and 56% as EU-TIRADS 5. Low-risk neoplasm cases were equally divided, with 50% being classified as EU-TIRADS 3 and the remaining 50% as EU-TIRADS 5. Among malignant cases, 13% were assessed as EU-TIRADS 3, 25% as EU-TIRADS 4, and a substantial 64% as EU-TIRADS 5. The classification and distribution of EU-TIRADS scores with postoperative pathology outcomes are presented in Table 1.

Analysis of Bethesda classifications revealed that 72% (n=15) of cases fell into category 3, while the remaining 28% (n=6) were classified under category 4. In our study, the incidence of malignancy among Bethesda 3 cases was lower at 27% (n:4), with 53% (n:8) being and 20% (n:3) classified as low-risk neoplasms. In contrast, Bethesda 4 cases exhibited a higher malignancy rate of 66% (n:4), with benign (n:1) and low-risk neoplasms (n:1) each constituting 17% of the cases. The data revealed a higher prevalence of malignancy in FNAB for Bethesda category 4 at 66% compared to 27% in Bethesda category 3 (p=0.20), as detailed in Table 2.

In the Bethesda 3 category, the radiological scoring revealed that 37% of benign cases were classified as EU-TIRADS 3, and 63% as EU-TIRADS 5. Among the malignant cases, 25% were scored as EU-TIRADS 3, 25% as EU-TIRADS 4, and 50% as EU-TIRADS 5. For the low-risk neoplasm group, 33% were assigned EU-TIRADS 3, and 67% EU-TIRADS 5 (Table 3). In the Bethesda 4 category, our radiological scoring identified EU-TIRADS 3 in one benign case. Additionally, one case with a low-risk neoplasm was also scored as EU-TIRADS 3. Among the malignant cases within this group, 25% were classified as EU-TIRADS 4, while the majority, 75%, were classified as EU-TIRADS 5. (Table 4). Notably, a statistically significant correlation was

observed in the Bethesda 4 group, indicating an increase in EU-TIRADS scoring concomitant with the exacerbation of postoperative pathology results (p=0.02, rs=0.87).

The postoperative pathological analysis demonstrated a median nodule size of 12 mm (ranging from 5 to 35 mm) in the malignant group, 25 mm (7 to 48 mm) in the benign group, and 23 mm (8 to 32 mm) in the low-risk neoplasm group, with the difference not reaching statistical significance (p=0.33), as illustrated in Figure 2. Lymph node metastasis was found in 24% of the cases overall, affecting 13% of cases in Bethesda category 3 and 60% in Bethesda category 4.

4.   DISCUSSION

Thyroid fine-needle aspiration (FNA) with ultrasound guidance is regarded as the most accurate test for diagnosing malignancy in thyroid nodules and reduces the need for surgery in benign nodules. It is important for clinicians to consider the individual patient's clinical and imaging features, as well as the specific histopathological diagnosis. The optimal management of thyroid nodules with a Bethesda III and IV cytology in pediatric patients is debatable due to the unpredictability of the cancer risk. This study represents the first comprehensive investigation in the existing literature that assesses the postoperative outcomes and explores the utility of EU-TIRADS scoring in the management of pediatric thyroid nodules categorized as Bethesda 3 and 4. To the best of our knowledge, this study is the first in-depth examination in the literature to evaluate postoperative results and assess the effectiveness of EU-TIRADS in managing pediatric thyroid nodules classified as Bethesda categories 3 and 4. The study evaluated twenty-one pediatric cases with Bethesda categories 3 and 4 and analyzed their EU-TIRADS scoring. Our results indicate that EU-TIRADS cannot provide guidance for FNA decisions in childhood. Additionally, it has been shown that the nodules detected with postoperative malignancy have smaller sizes and that small nodules can also be malignant. And the Bethesda 4 category findings is the statistically significant correlation between higher EU-TIRADS scores and the risk of malignancy development is higher in cases with SFN cases.

Within the scope of pediatric EU-TIRADS usage, the body of research remains notably sparse. Examination of existing studies, such as the one by Fernandez et al.(17), reveals a rather small cohort for cases categorized under Bethesda 3 and 4, limiting the breadth of their conclusions. Further, the literature review, including the work of Tuli et al.(18) and. Scappaticcio et al. (19) , which utilizes the SIAPC classification for FNAB pathologies, categorizes cases into benign or malignant outcomes. Both studies demonstrate a suboptimal performance in the management of pediatric patients with thyroid nodules. Our study aims to address the clinical challenges posed by Bethesda 3 and 4 thyroid nodules, with a goal to enrich the literature with insights specifically targeting these ambiguous categories in the pediatric population.

Within our investigation, 53% of the nodules classified as Bethesda 3 were determined to have benign pathologies postoperatively. This finding is corroborated by Canberk et al.'s (20), substantial cohort study, which identified 67% of AUS instances as benign. These concurrent findings raise questions about the American Thyroid Association's (ATA) stance in favor of prompt surgical involvement for AUS/FLUS nodules (2). Since fine needle aspiration biopsy (FNAB) alone is insufficient for definitive surgical decision-making, supplemental radiological evidence is necessary for guidance.

In our study, the postoperative results of AUS/FLUS cases showed 27% malignancy rate while SFN cases showed 66% malignancy rate. In 2019, Cherella et al. reported malignancy rates of 44% and 71% for AUS and SFN nodules, respectively(4). Published pediatric studies show that the malignancy rates for Bethesda 3 nodules range from 8.3% to 44% (4,21–23) and for Bethesda 4 nodules range from 35% to 100%(23–25). These studies suggest that the rates of malignancy both groups have been different rates but the risk of malignancy in pediatric patients with Bethesda 4 nodules is relatively high compared to Bethesda 3.

Multiple ultrasound scoring systems are available to categorize nodules for fine-needle biopsy (FNB) indications, including fine-needle cytology (10,26).

In the study by Borysewicz-Sańczyk et al. (27) conducted in Poland, a 29% malignancy rate was found among 17 cases with Bethesda categories 3-4-5-6. While all cases classified as Bethesda 5 and 6 were confirmed malignant postoperatively, two cases categorized as Bethesda 4 and labeled as high suspicion according to ATA classification were reported benign histopathological. Additionally, none of the six Bethesda 3 cases, deemed low suspicion, were found to have malignancy. Conversely, Richman et al.'s(28) study evaluated the ACR TI-RADS against ATA guidelines in pediatric thyroid nodule management. Their findings indicated that while ACR TI-RADS may decrease the biopsy rate of benign nodules, it might also result in a significant number of pediatric cancers not being biopsied (22.1%), suggesting potential inadequacy of ACR TI-RADS in pediatric cases. The high frequency of our benign cases classified as EU-TIRADS 5 may lead to unnecessary FNAB procedures. While most of our malignant cases align with EU-TIRADS 4-5, 13% of cases were classified as low-risk, a lower proportion than the 22% reported in Richman et al.'s (28) study evaluating ACR-TIRADS. This suggests that while EU-TIRADS corresponds with recognized literature in identifying higher-risk cases, there may be a discrepancy in the classification of lower-risk malignancies, indicating a potential area for review or adjustment in classification criteria. And also, in the study conducted by Creo et al.(29), malignant nodules were primarily identified within the ATA's high or intermediate suspicion groups. The study concluded that pediatric

radiologists' overall impressions were similarly sensitive but more specific than ATA risk stratification. They concluded that no ultrasound-based method perfectly separated benign from malignant nodules, affirming the ongoing necessity for FNAB in cases of suspicious nodules.

In Fernandez et al.' s (17) investigation, an evaluation of 31 pediatric thyroid nodules, Bethesda classification was applied, with categories ranging from 1 to 5, and 14 nodules underwent surgery, 6 of which were malignant. While 16% (n=5) of the cases were Bethesda 3 without postoperative malignancy, 6.52% (n=2) were Bethesda 4 with malignancy found. All malignant nodules were categorized as EU-TIRADS 4 or 5. The study highlighted the limitations of the case number but found EU-TIRADS classification had a sensitivity of 100%, specificity of 25%, PPV of 44%, and NPV of 100%, making it a reliable diagnostic tool for FNAB decision-making. In our analysis, which exclusively encompassed cases classified as Bethesda 3 and 4, we observed a notably larger sample size compared to prior research. In our study, 25% of the 15 cases classified as Bethesda 3 were malignant and exhibited radiological assessments consistent with EU-TIRADS 3-4-5. In the Bethesda 4 group, which comprised 6 cases, the malignancy rate was 66%, with all cases radiologically assessed as EU-TIRADS 4-5. When evaluating both studies, it appears that EU-TIRADS scoring provides a more dependable guide for fine needle aspiration biopsy (FNAB) in cases classified as Bethesda 4. However, this level of reliability does not extend to the Bethesda 3 category, where EU-TIRADS scoring does not exhibit the same predictive strength for FNAB decision-making.

Our findings indicate that in Bethesda 3 cases, the presence of EU-TIRADS 5 scores is lower in malignant cases, whereas it is higher in the low-risk and benign groups. In Bethesda 4 cases, a positive correlation is observed between EU-TIRADS scores and the deterioration of postoperative pathology outcomes. These findings emphasize the intricate relationship between EU-TIRADS scoring, Bethesda categories, and postoperative pathology outcomes.

Our results suggest that the size of nodules in the malignant group tends to be smaller compared to the benign and low-risk neoplasm groups but not statistically significant. The range of sizes within each group is also quite varied. Nodules classified as TBSRTC category IV and V are recommended for surgical resection due to their high risk of malignancy. For nodules with TI-RADS scores less than or equal to 3, ultrasound surveillance instead of FNA can be performed (30).The study retrospectively assessed the effectiveness of three ultrasound risk stratification systems (ACR-TIRADS, ATA, and EU-TIRADS) in pediatric patients with thyroid nodules and a history of radiation exposure. With 52 patients, 27% had papillary thyroid cancer (PTC) upon final histology. The systems showed high specificity (95–97%) and negative predictive value (88–93%), but they failed to recommend biopsies in a significant number of PTC cases, often due to nodules being smaller than 1 cm. The study suggests that while these systems are reliable, they could be improved by adjusting the size criteria for biopsy recommendations(31). It's important to note that nodule size alone is not a definitive indicator of malignancy, and other factors such as imaging characteristics and biopsy results should also be considered.

Study Limitations

Limitations of this study include the small sample size, data collection from a single center, and the need for postoperative follow-up results. So, we need more in-depth studies with larger sample sizes and results from long-term follow-ups.

5.   CONCLUSION

The optimal management of AUS/FLUS and FN/SFN thyroid nodules in children is still an area of active research, and it should be individualized based on factors such as the patient's age, the size and characteristics of the nodule, and the results of diagnostic fine needle aspiration biopsy. The postoperative pathology assessment unveiled a discernible variability in EU-TIRADS scores. Specifically, within the Bethesda 3 category, instances of malignancy exhibited a comparatively diminished percentage of EU-TIRADS 5, in contrast to its more pronounced occurrence within the low-risk and benign cohorts. Conversely, among Bethesda 4 cases, there emerged a conspicuous ascending trajectory in EU-TIRADS scores concomitant with a worsening trend in postoperative pathology outcomes. These findings accentuate the nuanced and debatable nature of the EU-TIRADS scoring system's utility in effectively guiding the intricate clinical decision-making process concerning pediatric thyroid nodules. The EU-TIRADS scoring system has the potential to be a useful tool for evaluating thyroid nodules in children, but its accuracy and effectiveness still require confirmation through additional research.

Statements

Acknowledgement

Statement of Ethics

Conflict of Interest Statement

Author Contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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Table 1. EU-TIRADS scoring of post-op pathology results

	EU-TIRADS 3	EU-TIRADS 4	EU-TIRADS 5	Total
Benign	44% (n:4)	0% (n:0)	56% (n:5)	100% (n:9)
Low-Risk Neoplasm	50% (n:2)	0% (n:0)	50% (n:2)	100% (n:4)
Malign	13% (n:1)	25% (n:2)	64% (n:5)	100% (n:8)
Total	33% (n:7)	10% (n:2)	57% (n:12)	100% (n:21)

Table 2. Pathology results of the cases according to post-operative WHO classification

	Post -operative pathology (WHO classification)		
	Benign (n:9)	*Low-risk Neoplasm (n:4)*	*Malign (n:8)*
Bethesda 3 (n:15)	53 % (n:8)	20 % (n:3)	27 % (n:4)
Bethesda 4 (n:6)	17 % (n:1)	17% (n:1)	66 % (n:4)
Total (n:21)	43 % (n:9)	19 % (n:4)	38 % (n:8)

Table 3. EU-TIRADS scoring of Bethesda 3 and post-op pathology results

Bethesda 3	EU-TIRADS 3	EU-TIRADS 4	EU-TIRADS 5	Total (n:15)
Benign	37% (n:3)	0% (n:0)	63% (n:5)	100% (n:8)
Low-Risk Neoplasm	33% (n:1)	0% (n:0)	67% (n:2)	100% (n:3)
Malign	25% (n:1)	25% (n:1)	50% (n:2)	100% (n:4)

Table 4. EU-TIRADS scoring of Bethesda 4 and post-op pathology results

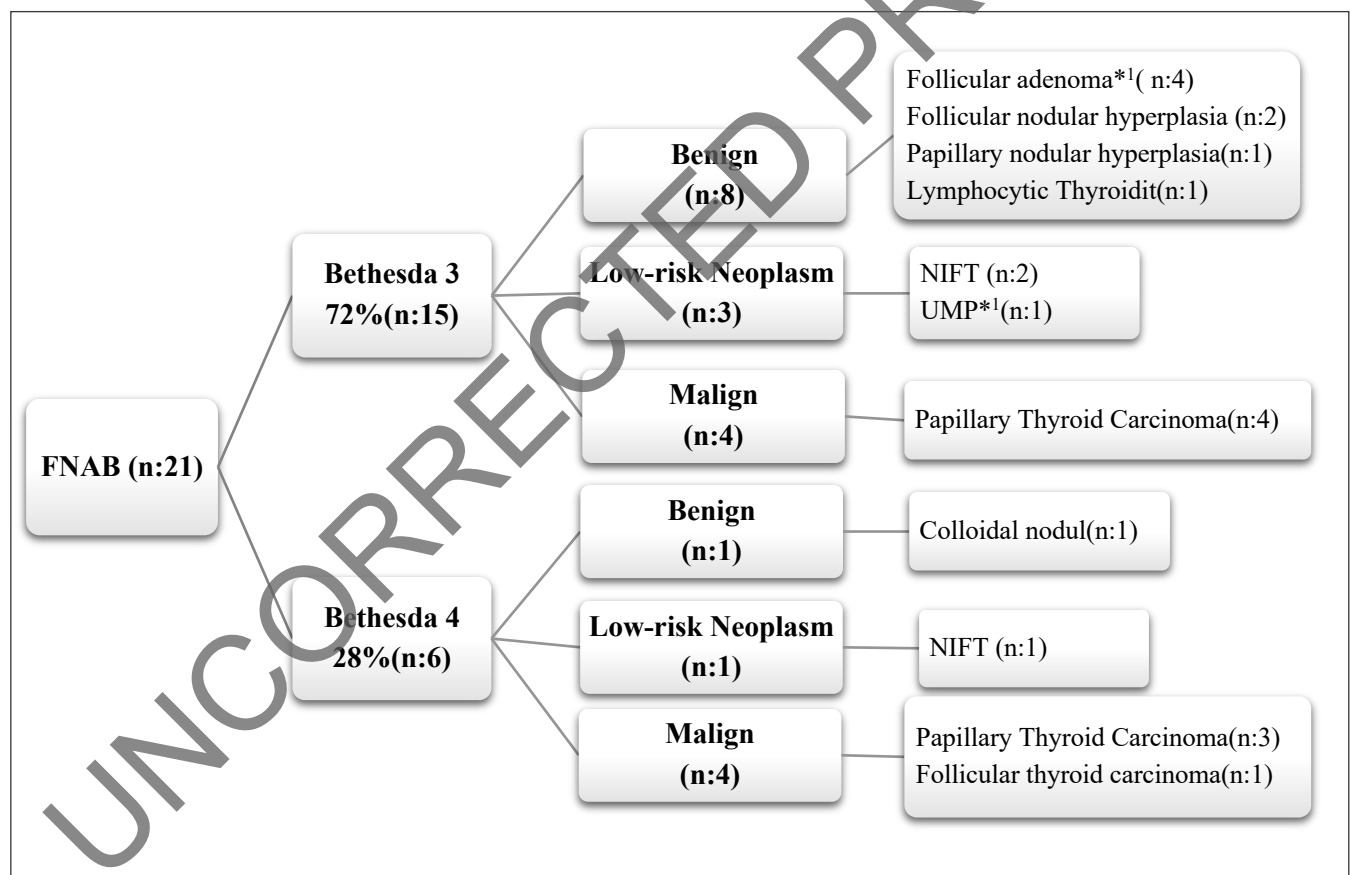| Bethesda 4	EU-TIRADS 3	EU-TIRADS 4	EU-TIRADS 5	Total (n:15)
Benign	**100% (n:1)**	0% (n:0)	0% (n:0)	100% (n:1)
Low-Risk Neoplasm	**100% (n:1)**	0% (n:0)	0% (n:0)	100% (n:1)
Malign	**0% (n:0)**	25% (n:1)	75% (n:3)	100% (n:4)

Figure 1. Postoperative pathology and FNAB results of the cases
NIFT: Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features
UMP: Thyroid Tumors of Uncertain Malignant Potential*(1=number of case)
AUS: Atypia of Undetermined Significance
FLUS: Follicular Lesion of Undetermined Significance
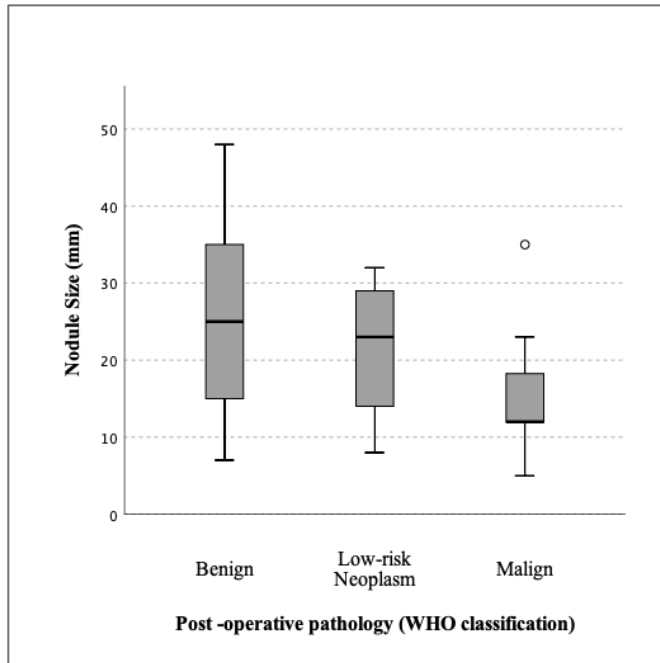**SFN:** Suspicious for Follicular Neoplasm

Figure 2. Nodule size (preoperative Thyroid USG) of post-op pathology results
*p value: 0.33