**Rate and Clinical Predictors of Malignancy in Thyroid Nodules with Indeterminate Cytology**

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**Background:** FNAC cannot differentiate between benign and malignant conditions in cytologically indeterminate thyroid lesions. Therefore, a minimum of diagnostic lobectomy is required for definitive diagnosis. The objective of this study is to identify the rate of malignancy and clinical features that may possibly predict malignancy in patients with these lesions, in Ethiopian hospitals.

**Methodology:** This was a retrospective review of the medical records of patients who underwent surgery for cytologically indeterminate thyroid lesions in three referral hospitals between September 2015 and September 2020.

**Results:** Of 85 patients with indeterminate cytology findings,56 (63.5%) were follicular, and 29 (34.1%) were reported to be hurthle cell neoplasms. Follicular lesions of undetermined significance (FLUS) and suspicious for follicular neoplasm were each reported in single cases (1.7%). Malignant disease was diagnosed in 19 (22.4%) of patients. Follicular variant of papillary cancer was detected in 7 (11.5%) patients. Hard nodule consistency was reported in 9 of 11 malignant lesions and 5 of 66 benign lesions. In multivariate binary logistic regression, hard nodule consistency was found to be associated with malignancy (p **0.012**, AOR=7.28(1.5, 34.54) 95% CI ). Ill-defined surface of a nodule was found to be associated with malignancy though the association was not statistically significant (P-value: 0.088, AOR 0.162(0.020, 1.313) 95% CI. Ultrasound evaluation of thyroid nodule was performed only in 41 (47.7%) of patients.

**Conclusion:** The rate of malignancy in thyroid nodules with indeterminate cytology was 22.4%. The risk of malignancy was higher in patients with hard thyroid nodule consistency and ill-defined surface. Despite the established benefits of ultrasound for evaluation of thyroid nodules, the current practice of its use in our setup is suboptimal.

**Key words:** *Follicular, hurthle cell, indeterminate cytology, predictors of malignancy*

# Introduction

FNAC of thyroid can generally differentiate between benign and malignant lesions except when the findings are suggestive of Atypia of undetermined significance (AUS), follicular lesion of undetermined significance (FLUS), suspicious of follicular neoplasm, follicular neoplasm or hurthle cell neoplasms (1,2). Follicular thyroid lesions are common cytological findings during evaluation of thyroid nodules.Differentiating follicular thyroid cancer & Hurthle cell cancer from thyroid adenoma cannot be made by FNAC alone rather it requires histological evidence of vascular and capsular invasion (2).

In 70-80% of cases, nodules with cytological diagnosis of follicular neoplasms turn out to be benign (2). For these reasons many patients with benign thyroid disease are subjected to potentially avoidable surgery (diagnostic lobectomy) and the associated cost. Likewise, the diagnostic confusion exposes patients with malignant disease that may potentially benefit from single initial total or near total thyroidectomy to undergo two surgeries. i.e., initial diagnostic Lobectomy and repeat surgery (completion thyroidectomy). Therefore, identifying factors that predict malignancy preoperatively may avoid the unnecessary surgeries, their cost and complications. Accordingly, there has been growing interest among researchers to predict malignancy preoperatively using different parameters such as clinical, ultrasound, cytological and molecular techniques (3–6). Intraoperative frozen section has been used in an attempt to define the adequate extent of surgery intraoperatively, but its routine use is quite limited (7). Despite these attempts, most of the results are inconsistent and sometimes contradictory. In developing nations, such as our country, decision making process is primarily clinical in part due to unavailability of advanced diagnostic modalities. Therefore, we seek to identify if there are clinical predictors of malignancy that can guide the choice and extent of therapy.

# Materials and Methods

This was a retrospective review of charts in patients who underwent thyroid surgery between September 2015 and September 2020 with initial FNAC diagnoses of follicular or hurthle cell neoplasm. Patients operated with the FNAC diagnosis of FLUS, AUS, follicular or hurthle cell neoplasm were selected from the operation room logbooks of Tikur Anbessa, Yekatit 12 and Zewditu memorial hospitals which are located in Addis Ababa, Ethiopia. Cases with recurrence or with inconclusive or lost biopsy results were excluded from the study.

FNACs and biopsy were reported by different pathologists from AAU, TASH or other institutions. Almost all FNA procedures were performed without ultrasound guidance. Demographic, clinical and laboratory data as well as pathology reports were reviewed from individual patient’s charts. The definitive diagnosis of malignancy was determined based on postoperative histopathological diagnosis. Sociodemographic data, mass characteristics including size, type of nodule and consistency as well as signs & symptoms such as rapid tumor growth, change of voice, dysphagia, airway obstruction, and duration of illness were analyzed for association with presence of malignancy. The Data analysis was made with SPSS version 24. Ethical approval was obtained from the research and ethics committee at the Department of surgery, Addis Ababa University.

**Operational definition**

**Consistency of swelling:** described as physical examination finding of the most senior examiner as firm, soft or hard.

**Size of nodule** was described in centimeters measured along its largest dimension. Duration of symptoms described in years when patients’ complaint was in less than a year it is stated infractions.

**Type of swelling**: described as physical examination finding of the most senior examiner as solitary, multinodular or diffuse goiter.

**Rapid growth:** subjective complaint of the patient claiming that there is recent fast growth of thyroid swelling.

**Intraoperative evidence of malignancy:** Intraoperative features including infiltration or fixity to surrounding structures /gross extrathyroidal extension, tumor thrombus in middle thyroid and/or jugular veins, lymph node involvement and fragile mass.

**Abbreviations**

AAU – Addis Ababa University

FN – Follicular neoplasm

FNAC–Fine needle aspiration cytology

HCC – Hurthle Cell Carcinoma

HCN – Hurthle Cell Neoplasm

OR – Odds Ratio

TASH – Tikur Anbessa Specialized Hospital

# Results

**Demographic Data**

The number of patients operated in the three hospitals with the diagnosis of follicular or hurthle cell thyroid neoplasm in 5 years were 115. Patients that fulfill the inclusion criteria were 85. FNA was taken without ultrasound guidance, in almost all of the patients. Follicular neoplasm was diagnosed in 56 (65.9%) and hurthle cell neoplasm in 29(34.1%)

Mean age of presentation was 35.64 + 12.823 (age range 18-78) years. Those patients with age <40 years were 70.6%, whereas age >60 was 5.9%. Seventy-four (87.1%) were female and 11 (12.9%) were male. Male to female ratio is 1:6.72. The vast majority of patients (77, 90.6%) were from Addis Ababa. The comparison between benign and malignant lesions is provided under **Table 1.**

**Table 1. Comparison of demographic data among patients with benign and malignant nodules**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables**  | **Benign nodules (66)** | **Malignant (19)**  | **P value** |
| Age at diagnosis (year) +SD | 36 + 13.2  | 34 + 11.3  |  |
| **Age category**  |  |  | 0.176 |
|  <40 | 72.70% | 63.20% |  |
|  **40-60**  | 19.7% | 36.8% |  |
|  >60 | 7.60% | 0% |  |
| **Sex: no (%)** |  |  |  **0.722** |
|  Male | 9(13.84%) | 2(11.76%) |  |
|  **Female**  | 56(86.15%) | 17(89.47%) |  |
|  M: F | 1:7.3 | 1:9.5 |  |
| **FNAC**:  |  |  |  |
|  **Hurthle cell neoplasm**  | **25(37.9%)** | **4(21.1%)** | **0.11** |
|  Follicular neoplasm |  |  |  |
|   **Thyrotoxicosis, No (%)** | 11(16.6%) | NO case | 0.706 |
|  |  |  |  |

**Clinical Presentation**

The mean duration of symptoms for all the patients was 4.68 + 6.28 (range, 15 days to 30 years). All patients had complaints of anterior neck swelling. None of the patients had history of exposure to radiation or family history of thyroid cancer. Other complaints presented as follows: pressure sensation 20(23.5%), history of rapid growth 11(12.9%), hoarseness of voice in 8(9.4%) difficulty of swallowing 5(5.9%), symptom of airway obstruction 1(1.2%). The comparison between the presentation of benign and malignant lesions is provided under **Table 2.**

**Table 2: Presenting symptoms among patients with benign and malignant thyroid nodules**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Symptoms: n (%)** | **Benign nodules (66)** | **Malignant (19)** | **Univariate****P value**  | **Multivariate****P value**  |
| Pressure sensation 16(18.8%) | 11 (68.75%) | 5(31.25%) |  0.347 |  |
| **Neck swelling 85(100%)** | **66(77.6%)** | **19(22.4%)** |  |  |
| Rapid Growth 11(12.9%) | 6(54.54%) | 5(45.45%) | **0.059** | **0.579** |
| **Change of voice 8(9.4%)** | **7(87.5%)** | **1(12.8%)** | **0.491** |  |
| Difficulty of swallowing 5(5.9%) | 4(80%) | 1(20%) |  0.897 |  |
| **Signs and symptoms of airway obstruction 1(1.2%)** | **0** | **1(100%)** |  **1** |  |
| Family history of thyroid cancer (0%) | 0 | 0 |  |  |
| **Radiation exposure to head and** **Neck (0%)** | **0** | **0** |   |  |
| **Mean duration of symptoms(years)** | **4.8+6.5, [0.04-30]** | **4.2+5.38, [0.08-20]** | **0.679** |
|  |  |  |  |  |

**Physical Examination Findings**

Among all thyroid nodules with indeterminate cytology, the mean size of the tumor was 4.77 + 2.21 cm, ranging from 1 cm to 15 cm. Based on size category, most patients (60, 70.6%) have size >3.0 cm. Multinodular goiter is the commonest type of swelling (59, 69.4%) followed by solitary nodule (23, 27.1%), and diffuse (3, 3.5%) swelling respectively. Firm consistency was the commonest (63, 74.1%) followed by hard in (14, 16.5%), and soft (8, 9.4%) consistencies respectively. Most swellings (70, 82.4%) have smooth nodule surface whereas 10(11.8%) of the nodules had irregular/rough surface. Missing values were 5(5.9%). Lymphadenopathy is seen in 3(3.5%) patients. Based on preoperative serum TSH level measurement, 73 (85.9%) of the patients were found to be euthyroid. Hypothyroidism is documented in 1(1.2%) whereas thyrotoxicosis in 11(12.9%). Physical findings in contrast to risk of malignancy are illustrated in **Table 3.**

**Table 3: Physical findings and predictors of malignancy determined by univariate &multivariate analysis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Nodule Characteristics  | Benign nodules (66) | Malignant (19) | Univariate P value | Multivariate P value |
| **Nodule consistency no (%)** |   |   | **<0.01** | **0.012** |
|  Hard 14(16.5%) | 5(35.7%) | 9(64.3%) |  |  |
|  Firm 63(74.1%) | 54(85.7%) | 9(14.3%) |  |  |
|  Soft 8(9.4%) | 7(87.5%) | 1(12.5%) |  |  |
| **Surface of the nodule, no (%)** |  |  | **<0.01** | **0.088** |
|  Irregular 10(11.8%) | 3(4.5%) | 7(36.8%) |  |  |
|  Smooth 70(82.4%) | 60(85.7%) | 10(14.3%) |  |  |
|  Missing 5(5.9%) | 3 | 2 |  |  |
| **Nodule size, cm** |  |  | 0.558 |  |
|  Mean + SD | 4.62+2.24 | 5.28+2.1 |  |  |
|  >3cm | 46 | 14 |  |  |
|  <3cm  | 19 | 4 |  |  |
|  Missing | 1 | 1 |  |  |
| **Type of nodule** |  |  | 0.626 |  |
|  MNG 59(69.4%) | 12(20.33%) | 47(79.66) |  |  |
|  Solitary 23(27.1%) | 7(30.43%) | 16(69.56%) |  |  |
|  Diffuse 3(3.5%) | 3(100%) | 0  |  |  |
| **Other characteristics**  |  |  |  |  |
|  Tenderness 4(4.7%) | 2(50%) | 2(50%) | 0.22 |  |
|  Fixity 2(2.4%) | 1(50%) | 1(50%) | 0.398 |  |
|  Lymphadenopathy 3(3.5%) | 2(66.66%) | 1(33.33%) | 0.677 |  |
|  |  |  |  |  |
| Intraoperative evidence of malignancy |  2(3.03%)  | 3(15.78%)  |  0.061   |  0.898 |

**Imaging**

Ultrasound of the thyroid, as investigation modality for nodule evaluation was used only in 39(45.8%) of the patients. The rest of patients have undergone surgery based on clinical assessment, evaluation of thyroid function and FNAC alone.

**Definitive diagnosis**

Definitive diagnosis of malignancy was made in 19(22.4%) cases by postoperative histopathology evaluation. The remaining 66(77.6%) were benign cases. Among the malignant lesions Papillary carcinoma is the leading 11 (12.94%) followed by Follicular carcinoma 5 (5.88%); Anaplastic cancer 2, (2.35 %); Hurthle cell cancer 1, (1.17%)

Hurthle cell neoplasm accounts for 8 cases (12.7%); Hurthle cell adenoma 7 (8.2%) and Hurthle cell carcinoma 1(1.2%,). Benign conditions consist of Follicular adenoma 30 (35.2%), Colloid goiter 24 (28.2%), Hashimoto thyroiditis 4 (4.7%) and Riedel thyroiditis 1, (1.17%). Comparison between cytologically indeterminate diagnosis and definitive diagnosis is stipulated on **Table 4**.

**Table 4:** Comparison between preoperative cytology and definitive diagnosis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | Pathology |  FN |  HCN |  Total |
| Malignant | Papillary cancer  | 10 | 1 | 11(12.9%) |
|  19(22.4%) | Follicular cancer | 4 | 1 | 5(5.8%) |
|  | Anaplastic cancer | 1 | 1 | 2(2.4%) |
|  | Hurthle cell carcinoma  | 0 | 1 | 1(1.2%) |
|  |  |  |  |  |
| Benign | Follicular adenoma | 18 | 8 | 26(32.9%) |
| 66(77.6%) | Colloid goiter  | 15 | 5 |  20(23.5%) |
|  | Hurthle cell adenoma  | 0 | 7 | 7(8.2%) |
|  | Adenomatoid hyperplasia  | 4 | 2 | 6(7.1%) |
|  | Riedel Thyroiditis  | 1 | 0 | 1(1.2%) |
|   | Hashimoto thyroiditis  | 1 | 3 | 4(4.7%) |

**Predictors of malignancy**

On univariate analysisrapid growth (p value: 0.049), hard consistency of a nodule and irregular surface of a nodule showed association (each with p value < 0.01). Other variables didn’t show any association with malignancy both in univariate, and bivariate analysis.

On multivariate analysis we have found that hard consistency is associated with thyroid malignancy with p-value of **0.012**, AOR=7.28(1.5, 34.54) 95% CI and irregular surface of the nodule found to have marginal association; P-value: 0.088, AOR 0.162(0.020, 1.313) 95% CI (T**able 3)**

# Discussion

FNA cytology is generally a reliable diagnostic test in differentiating between benign and malignant thyroid lesions except in cytologically indeterminate lesions. The Bethesda System is the most widely used and standardized tool for communication of thyroid cytopathology (1). FLUS, AUS, follicular neoplasms and hurthle cell neoplasms are considered to be cytologically indeterminate. In these group of lesions, accurate distinction between benign and malignant disease cannot be made as cytology analyzes only individual cell characteristic without basement membrane, and the difference depends on the presence and absence of architectural features of capsular and vascular invasion.

A diagnosis of follicular neoplasm accounted for 63.5 % of the indeterminate cytology whereas hurthle cell neoplasm was 34.1%. Single cases of FLUS and Suspicious of Follicular Neoplasm were also found. Our study found an over diagnosis of hurthle cell neoplasm (34.1%) on preoperative cytology compared to less than 12 % in other studies (10,13). HCNs are considered as variants of follicular neoplasms by many authors (14). However, WHO classification considers Hurthle cell tumors as separate entity due to their peculiar genetic profiles, biological profiles and clinical features (15). The risk of malignancy is thought to be higher in these lesions compared to follicular neoplasms (16). But this is challenged by others as there is no increased risk (17,18).

Hurthle cells can be found in different reactive, inflammatory and neoplastic processes of the thyroid. For a lesion to be diagnosed as HCN, it should be predominantly constituted of hurthle cells and encapsulated. The amount of hurthle cells required for the diagnosis of HCN has been defined variably in the literature. Most authors state 75% (8–10) or 50% (11,12) as defining value. In our setup pathologists use variable cutoff value. In the present study, only 8 out of 29 cytologically diagnosed hurthle cell neoplasms were truly HCN on definitive pathology diagnosis and only 1 of 29 cytologically diagnosed HCN neoplasms turned out to be HCC. Therefore, in our institutions, cytologic diagnosis of HCN is not reliable and it is not associated with increased risk of malignancy though the number of definitively diagnosed HCNs is small so as to make any meaningful statistical correlation.

Common biopsy findings after thyroidectomy for cytologically indeterminate thyroid lesions include Follicular adenoma, adenomatoid hyperplasia, follicular carcinoma, follicular variant of papillary cancer and classical papillary cancer (8,10,13)**.** The incidence of malignancy in cytologically indeterminate nodules ranges from 14% to 48.5% (8,10,13,17). The incidence of malignancy in the present study was 22.4%; which is comparable with most of the reports.

Follicular variant of papillary cancer, classical papillary cancer and follicular thyroid cancers are malignancies that are commonly found in such lesions (10,13,19). Rarely, others such as medullary and anaplastic cancers have been reported (20)(13). Likewise, in the present study, follicular variant of papillary cancer was the leading which accounted for 7 out of 19 malignant nodules followed by follicular thyroid cancer (5/19). The total number of papillary cancer cases including the classical variant was 11.

Different clinical features have been described as predictors of malignancy in thyroid nodules. These includes history of hoarseness of voice, history of rapid growth of the nodule, fixation to surrounding structures, hard consistency of the nodule and ill-defined surface of the nodule (21,22). Furthermore, old age, male sex, solitary nodule and larger size of nodule are thought to be associated with increased cancer risk of malignancy (13,23). In contrary, others reported that old age, male sex, larger nodule size, and solitary nodule are not predictive of malignancy (4,24). Large nodule size has been defined variably among different researchers including >3cm (13), >4cm (4). In the present study, we arbitrarily used the earliest. Only hard consistency of a nodule on physical examination has been found to be associated with malignancy. Of the 15 nodules that were hard at palpation 9(64.3%) were malignant. High rates of malignancy in hard nodules were reported in other studies where the study group were not limited to indeterminate cytology (25,26).

Ill-defined surface of a nodule, usually assessed by ultrasound, is suggested to be associated with malignancy (27,28). In the present study, ill-defined surface of a nodule(irregularity) was documented based on physical examination finding only. However, there was marginal correlation with malignancy, though it was not statistically significant. Albeit there was no association with larger size, it can be noted that the mean size was slightly larger in malignant nodules.

Sonographic features such microcalcification, hypoechoic pattern, irregular borders; high serum thyroglobulin concentration, genetic markers, as well as molecular markers such as BRAF, galectin-3, RAS, RET/PTC and cytokeratin are associated with high risk of malignancy (4,8,29,30). In our series only 45.8% of patients had ultrasound done for evaluation of thyroid nodule. Most of them didn’t document complete description of a nodule. Similarly, none of the patients had serum Thyroglobulin determined as it is not readily available in our country. The same thing is true for genetic and molecular means. Therefore, we couldn’t analyze these parameters as predictors of malignancy.

Though its reliability is questionable frozen section is sometimes used to identify malignancy intraoperatively and hence define the extent of surgery (7,24). We attempted to evaluate intraoperative clinical evidences of malignancy as frozen section evaluation is not available in our setup. It was demonstrated in total of 5 patients. Among which 3 cases had malignancy. One of the 5 patients had extensive fixity of the nodule to the surrounding structures; hence malignancy was considered intraoperatively though nothing more than debulking could be done. Eventually, post-operative biopsy revealed Riedel thyroiditis.

Certain risk factors for development of thyroid cancer include being exposed to ionizing radiation at a young age, having a first-degree relative with thyroid cancer and chronic TSH stimulation in endemic goitrous areas (31,32). None of these were identified in our group of patients.

We attempted to find out if the patients are from endemic area. Unfortunately, it was not possible to determine that because many patients registered only their tentative address during treatment period (not the permanent address of their residence). Accordingly, about 90% of the patients appeared to be from Addis Ababa, which is iodine sufficient. Therefore, meaningful association could not be assessed. Similarly, we had only one patient with high serum TSH who was already on treatment.

FNAC was done at different institutions by different professionals with different level of experience.in addition, immunohistochemical markers were not available. Accordingly, the reports documented on report papers had different level of details. For these reasons we couldn’t analyze its role as an independent predictor of malignancy. Similarly, ultrasound was excluded as it was not done in most of the patients or due to inadequate reports whenever it is done. Future prospective studies addressing such limitations can have a paramount importance.

# Conclusion

The rate of malignancy in thyroid nodules with indeterminate cytology was 22.4%. Hard nodule consistency on physical examination is found to be associated with increased risk of thyroid malignancy. Irregular surface of a nodule is marginally associated with malignancy. However other clinical parameters such as older age, large nodule size, and solitary nodule didn’t show any association. FNAC is found to be inaccurate on differentiating between hurthle cell and follicular neoplasms. The routine uses of ultrasound for the evaluation of thyroid nodule with cytological diagnosis of follicular or hurthle cell neoplasms in Ethiopian hospitals is low.

# Recommendations

In resource poor settings, where patients present late, hard consistencyof the nodule on palpation can be considered predictor of malignancy in patients with cytologically indeterminate thyroid nodules. Hence, it can be used in risk stratification and decision making on the extent of Surgery. The role of different clinical parameters stated to be useful for risk stratification in follicular and hurthle cell neoplasms should be studied by high quality prospective researches. The use of ultrasound both for evaluation and guiding FNAC of thyroid swelling may need to be encouraged.

# DECLERATION

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**Conflict of interest**All authors declared that there is no competing interest.

**Authors approval**The manuscript has been read and approved by all authors

**Availability of data and materials**A soft copy of all data used for this article are available from the corresponding author, it can be made available up at a reasonable request.

**Ethics approval**The study was approved by the Research & Ethical committee of department of surgery College of health science, Addis Ababa University.

# References

1. Theoharis CGA, Schofield KM, Hammers L, Udelsman R, Chhieng DC. The Bethesda Thyroid Fine-Needle Aspiration Classification System: Year 1 at an Academic Institution. Thyroid. 2009 Nov;19(11):1215–23.

2. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2017 Nov;27(11):1341-1346. doi: 10.1089/thy.2017.0500. PMID: 29091573.

3. Davis NL, Gordon M, Germann E, Robins RE, McGregor GI. Clinical parameters predictive of malignancy of thyroid follicular neoplasms. Am J Surg. 1991 May;161(5):567–9.

4. Gulcelik NE, Gulcelik MA, Kuru B. Risk of Malignancy in Patients With Follicular Neoplasm: Predictive Value of Clinical and Ultrasonographic Features. Arch Otolaryngol Neck Surg. 2008 Dec 15;134(12):1312.

5. Melck AL, Yip L. Predicting malignancy in thyroid nodules: Molecular advances. Eisele DW, editor. Head Neck. 2012 Sep;34(9):1355–61.

6. Hawasli A, Rizzo P, Khoury H, McCaffrey JL. Can Fine-Needle Aspiration Biopsy of Thyroid Nodule Help in Determining the Extent of Surgery in Follicular and Hurthle Cell Neoplasm at a Community Teaching Institution? :1.

7. Najah H, Tresallet C. Role of frozen section in the surgical management of indeterminate thyroid nodules. Gland Surg. 2019 Aug;8(Suppl 2):S112–7.

8. Lee KH, Shin JH, Ko ES, Hahn SY, Kim JS, Kim J-H, et al. Predictive factors of malignancy in patients with cytologically suspicious for Hurthle cell neoplasm of thyroid nodules. Int J Surg. 2013 Nov;11(9):898–902.

9. R. Kroeker T, Prisman E, D. Shah M, MacMillan C, L. Freeman J. Hurthle Cell Lesions- A Retrospective Review of Final Surgical Pathology. J Thyroid Disord Ther [Internet]. 2014 [cited 2020 Aug 16];03(02). Available from: http://www.omicsgroup.org/journals/hurthle-cell-lesions-a-retrospective-review-of-final-surgical-pathology-2167-7948-3-155.php?aid=25626

10. McHenry CR, Thomas SR, Slusarczyk SJ, Khiyami A. Follicular or Hu ̈rthle cell neoplasm of the thyroid: Can clinical factors be used to predict carcinoma and determine extent of thyroidectomy? Surgery. 1999 Oct;126(4):798–804.

11. Melck A, Bugis S, Baliski C, Irvine R, Anderson DW, Wilkins G, et al. Hemithyroidectomy: the preferred initial surgical approach for management of Hurthle cell neoplasm. Am J Surg. 2006 May;191(5):593–7.

12. Hudak K, Mazeh H, Sippel RS, Chen H. Hürthle cell metaplasia on fine-needle aspiration biopsy is not by itself an indication for thyroid surgery. Am J Surg. 2012 Mar;203(3):287–91.

13. Baloch ZW, Fleisher S, LiVolsi VA, Gupta PK. Diagnosis of ?follicular neoplasm?: A gray zone in thyroid fine-needle aspiration cytology. Diagn Cytopathol. 2002 Jan;26(1):41–4.

14. Ahmadi S, Stang M, Jiang XS, Sosa JA. Hürthle cell carcinoma: current perspectives. OncoTargets Ther. 2016;9:6873–84.

15. Lloyd RV, Osamura RY, Kloppel G, Rosai J (editors) €. WHO Classification of Tumours of Endocrine Organs, . Lyon, France: . 4th edn. IARC; 2017.

16. Zdon MJ, Fredland AJ, Zaret PH. Follicular Neoplasms of the Thyroid: Predictors of Malignancy? :1.

17. Öz B, Doğan S, Emek E, Akyüz M, Akcan A, Sözüer E, et al. Predictive Factors of Malignancy in Cytology of Indeterminate Follicular and Hürthle Cell Neoplasms of the Thyroid Gland. Int Surg. 2019 Apr 1;103(1–2):9–14.

18. Ren Y, Kyriazidis N, Faquin WC, Soylu S, Kamani D, Saade R, et al. The Presence of Hürthle Cells Does Not Increase the Risk of Malignancy in Most Bethesda Categories in Thyroid Fine-Needle Aspirates. Thyroid. 2020 Feb 4;30(3):425–31.

19. Lee SH, Baek JS, Lee JY, Lim JA, Cho SY, Lee TH, et al. Predictive Factors of Malignancy in Thyroid Nodules with a Cytological Diagnosis of Follicular Neoplasm. Endocr Pathol. 2013 Dec;24(4):177–83.

20. Doddi S, Chohda E, Maghsoudi S, Sheehan L, Sinha A, Chandak P, et al. The final outcome of indeterminate cytology of thyroid nodules in a District General Hospital. Il G Chir. 2015 Jun;36(3):122–7.

21. Mittal M, Ganakumar V, Shukla R, Kumar Garg M. Thyroid Nodule: Approach and Management. In: Agrawal NK, editor. Goiter - Causes and Treatment [Internet]. IntechOpen; 2020 [cited 2020 Nov 30]. Available from: https://www.intechopen.com/books/goiter-causes-and-treatment/thyroid-nodule-approach-and-management

22. Schlinkert RT, Van Heerden JA, Goellner JR, Gharib H, Smith SL, Rosales RF, et al. Factors That Predict Malignant Thyroid Lesions When Fine-Needle Aspiration Is “Suspicious for Follicular Neoplasm.” Mayo Clin Proc. 1997 Oct;72(10):913–6.

23. Trimboli P, Condorelli E, Catania A, Sorrenti S. Clinical and ultrasound parameters in the approach to thyroid nodules cytologically classified as indeterminate neoplasm. Diagn Cytopathol. 2009 Oct;37(10):783–5.

24. You SH, Jung CK, Chae BJ, Song BJ, Jung SS, Bae JS. Predictive Factors of Malignancy in Thyroid Nodules Diagnosed as Follicular Neoplasm or Hürthle Cell Neoplasm on FNA. Korean J Endocr Surg. 2012;12(4):231.

25. Christensen SB, Bondeson L, Ericsson UB, Lindholm K. Prediction of malignancy in the solitary thyroid nodule by physical examination, thyroid scan, fine-needle biopsy and serum thyroglobulin. A prospective study of 100 surgically treated patients. Acta Chir Scand. 1984;150(6):433–9.

26. Dedivitis R, do Couto Netto S, de Castro M, Pfuetzenreiter E, Nardi C, de Barbara E. Predictive Value for Malignancy of the Thyroid Nodule Macroscopically. Arq Int Otorrinolaringol. 2014 Feb 13;14(02):225–30.

27. Moon W-J, Jung SL, Lee JH, Na DG, Baek J-H, Lee YH, et al. Benign and malignant thyroid nodules: US differentiation--multicenter retrospective study. Radiology. 2008 Jun;247(3):762–70.

28. Takashima S, Fukuda H, Nomura N, Kishimoto H, Kim T, Kobayashi T. Thyroid nodules: re-evaluation with ultrasound. J Clin Ultrasound JCU. 1995 Apr;23(3):179–84.

29. Bartolazzi A, Orlandi F, Saggiorato E, Volante M, Arecco F, Rossetto R, et al. Galectin-3-expression analysis in the surgical selection of follicular thyroid nodules with indeterminate fine-vgneedle aspiration cytology: a prospective multicentre study. Lancet Oncol. 2008 Jun;9(6):543–9.

30. Nikiforov YE, Steward DL, Robinson-Smith TM, Haugen BR, Klopper JP, Zhu Z, et al. Molecular Testing for Mutations in Improving the Fine-Needle Aspiration Diagnosis of Thyroid Nodules. J Clin Endocrinol Metab. 2009 Jun 1;94(6):2092–8.

31. Iodine and cancer. Thyroid 2001 May115483-6 Doi 10108910507250130017643.

32. Haipeng Xiao. Review of Factors Related to the Thyroid Cancer Epidemic. Liu Su Xiao H Rev Factors Relat Thyroid Cancer Epidemic Int J Endocrinol 201720175308635 Doi10115520175308635.