Research Article

Rate and clinical predictors of malignancy in thyroid nodules with indeterminate cytology

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Abstract

Background: Fine needle aspiration cytology (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.

Methods: 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, 54 (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. A follicular variant of papillary cancer was detected in 7 (8.23%) patients. Hard nodule consistency was reported in 9 of 19 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). The ill-defined surface of a nodule was found to be associated with malignancy though the association was not statistically significant ($P = 0.088$, AOR = 0.162 (0.020, 1.313) 95% CI. Ultrasound evaluation of thyroid nodule was performed only in 39 (45.8%) 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 the evaluation of thyroid nodules, the current practice of its use in our setup is suboptimal.

Keywords: Follicular; hurthle cell; indeterminate cytology; predictors of malignancy

INTRODUCTION

FNAC of the 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 the 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]. Many patients with benign thyroid disease are thus

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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 a 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 unnecessary surgery, along with its 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]. The 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, the decision-making process is primarily clinical in part due to the 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 cross-sectional review of charts in patients who underwent thyroid surgery between September 2015 and September 2020 for cytologically indeterminate thyroid nodules. All patients operated with the FNAC diagnosis of FLUS, AUS, hurtle cell neoplasm, suspicious for follicular neoplasm or follicular 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.

FNAC and biopsy were reported by different pathologists from AAU, TASH, or other institutions. Almost all FNA procedures were performed without ultrasound guidance. The Bethesda system was used to classify the FNA results. Definitive diagnosis of malignancy was determined based on the postoperative histopathological diagnosis. Demographic, clinical, and laboratory data as well as pathology reports were reviewed from individual patient charts. Sociodemographic data, mass characteristics including size, surface, consistency, and type of nodule 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 the presence of malignancy. SPSS version 24 was used for data analysis.

Categorical data were presented as percentages and frequencies of occurrence. Continuous variables were described as means and standard deviations Associations between categorical variables were checked with chi-square test. Univariately associated variables were subjected to multivariate analysis

The degree of association was calculated using binary logistic regression, with a statistically significant cut-off ($P < 0.05$).

Ethical approval was obtained from the research and ethics committee at the Department of Surgery, Addis Ababa University.

RESULTS

Demographic data

The number of patients operated on in the three hospitals with the diagnosis of follicular or hurtle cell thyroid neoplasm in 5 years was 115. Patients that fulfill the inclusion criteria were 85. FNA was taken without ultrasound guidance, in almost all of the patients. The follicular neoplasm was diagnosed in 54 (63.5%) and hurtle cell neoplasm in 29 (34.1%)

The mean age of presentation was 35.64 + 12.823 (age range 18-78) years. Among all patients, 70.6% were younger than 40 while 5.9 % were older than 60. 74 (87.1%) were female and 11 (12.9%) were male. The 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 in Table 1 below.

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 a history of exposure to radiation or a family history of thyroid cancer. Other presenting complaints were 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%), a symptom of airway obstruction 1 (1.2%). The comparison between the presentation of benign and malignant lesions is provided below in Table 2.

Physical examination findings

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

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

Variables	Benign nodules (*n* = 66)	Malignant (*n* = 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	19.70%	36.80%	
>60	7.60%	0.00%	
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 (37.90%)	4 (21.10%)	0.110
Follicular neoplasm			
Thyrotoxicosis, no (%)	39 (59%)	15 (79%)	0.706

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 (77.60%)	19 (22.40%)		
Rapid Growth 11 (12.9%)	6 (54.54%)	5 (45.45%)	0.059	0.579
Change of voice 8 (9.4%)	7 (87.50%)	1 (12.80%)	0.491	
Difficulty of swallowing 5 (5.9%)	4 (80.00%)	1 (20.00%)	0.897	
Signs and symptoms of airway obstruction 1 (1.2%)	0	1	1.000	
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	

goiter is the commonest type of swelling (59, 69.4%) followed by solitary nodule (23, 27.1%), and diffuse (3, 3.5%) swelling. Firm consistency was the commonest (63, 74.1%) followed by hard (14, 16.5%), and soft (8, 9.4%) consistency. Most swellings (70, 82.4%) have smooth nodule surface whereas 10 (11.8%) of the nodules had irregular/ill-defined surfaces. The surface was not described in 5 (5.9%) patients 'charts. 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 relation to the risk of malignancy are illustrated in Table 3.

Imaging

Ultrasound of the thyroid, as an investigation modality for nodule evaluation, was used only in 39 (45.8%) patients. The rest of the patients underwent 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 malignancy (11, 12.9%) followed by follicular carcinoma (5, 5.88%); anaplastic cancer (2, 2.35%); hurthle cell cancer (1, 1.17%). One of the five follicular carcinomas was a minimally invasive encapsulated variant.

Hurthle cell neoplasm accounts for 8 cases (9.4%); hurthle cell adenoma 7 (8.2%) and hurthle cell carcinoma 1 (1.2%,). Benign conditions consisted of follicular adenoma (30, 35.2%), colloid goiter (24, 28.2%),

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

Nodule Characteristics (*n* = 85)	Benign nodules (66)	Malignant (19)	Univariate *P*-value	Multivariate *P*-value
Nodule consistency no (%)			< 0.01	0.012
Hard 14 (16.5%)	5 (35.70%)	9 (64.30%)		
Firm 63 (74.1%)	54 (85.70%)	9 (14.30%)		
Soft 8 (9.4%)	7 (87.50%)	1 (12.50%)		
Surface of the nodule, no (%)			< 0.01	0.088
Ill-defined 10 (11.8%)	3 (30.00%)	7 (70.00%)		
Smooth 70 (82.4%)	60 (85.70%)	10 (14.30%)		
Missing 5 (5.9%)	3	2		
Nodule size, cm			0.558	
Mean + SD	4.62 + 2.24	5.28 + 2.10		
> 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	0		
Other characteristics *n* (%)				
Tenderness 4 (4.7%)	2	2	0.220	
Fixity 2 (2.4%)	1	1	0.398	
Lymphadenopathy 3 (3.5%)	2	1	0.677	
Intraoperative evidence of malignancy 5 (5.9%)	2	3	0.061	0.898

Table 4. Comparison between preoperative FNA diagnosis and biopsy results.

	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%)

Hashimoto thyroiditis (4, 4.7%), and Riedel thyroiditis (1, 1.2%). Comparison between cytologically indeterminate diagnosis and postoperative definitive diagnosis with biopsy is depicted in Table 4.

Predictors of malignancy

On univariate analysis, rapid growth (P = 0.049), hard consistency of a nodule, and irregular surface of a nodule showed association (each with $P < 0.01$). 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 a 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 = 0.088, AOR = 0.162 (0.020, 1.313) 95% CI (Table 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 the communication of thyroid cytopathology [1]. FLUS, AUS, follicular neoplasms, and hurthle cell neoplasms are considered to be cytologically indeterminate. In this group of lesions, an accurate distinction between benign and malignant disease cannot be made as cytology analyzes only individual cell characteristics 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 overdiagnosis of hurthle cell neoplasm (34.1%) on preoperative cytology compared to less than 12% in other studies [8, 9]. HCNs are considered variants of follicular neoplasms by many authors [10]. However, WHO classification considers Hurthle cell tumors as a separate entity due to their peculiar genetic profile, biological profile, and clinical features [11]. The risk of malignancy is thought to be higher in these lesions compared to follicular neoplasms [12]. But this is challenged by others [13, 14].

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 encapsu-lated and predominantly consist of hurthle cells. The amount of hurthle cells required for the diagnosis of HCN has been defined variably in the literature. Most authors state 75% [8, 15, 16] or 50% [17, 18] as a defining value. In our setup, pathologists use variable cutoff values. 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. Although, the number of definitively diagnosed HCNs is too small in order 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, 9, 15]. The incidence of malignancy in cytologically indeterminate nodules ranges from 14% to 48.5% [8, 9, 13, 15]. The incidence of malignancy in the present study was 22.4%; which is comparable with most of the reports.

Follicular variants of papillary cancer, classical papillary cancer, and follicular thyroid cancers are malignancies that are commonly found in such lesions [8, 9, 19]. Rarely, others such as medullary and anaplastic cancers have been reported [9, 20]. Likewise, in the present study, the follicular variant of papillary cancer was the leading type, 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 include the history of hoarseness of voice, history of the rapid growth of the nodule, fixation to surrounding structures, hard consistency of the nodule, and the ill-defined surface of the nodule [21, 22]. Furthermore, old age, male sex, solitary nodule, and larger size of the nodule are thought to be associated with increased risk of malignancy [9, 23]. In contrast, 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 [9], > 4cm [4]. In the present study, we arbitrarily used the former. Only the hard consistency of a nodule on physical examination was found to be associated with malignancy. Of the 15 nodules that were hard on palpation 9 (64.3%) were

malignant. High rates of malignancy in hard nodules were reported in other studies where the study group was not limited to indeterminate cytology [25, 26].

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

Sonographic features (such as 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 a high risk of malignancy [4, 15, 29, 30]. In our series, only 45.8% of patients had an ultrasound done for evaluation of thyroid nodule. Most of these didn't document a complete description of a nodule. 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, the frozen section is sometimes used to identify malignancy intraoperatively and hence define the extent of surgery [7, 24]. We attempted to evaluate intraoperative clinical evidence of malignancy as frozen section evaluation is not available in our setup. Intraoperative features of malignancy were present in a total of 5 patients, among which 3 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, a post-operative biopsy revealed Riedel thyroiditis.

Certain risk factors for the 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 our patients had these risk factors.

We attempted to find out if the patients are from an endemic area. Unfortunately, it was not possible to determine that because many patients registered only their tentative address during the 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, the meaningful association could not be assessed. Likewise, we had only one patient with high serum TSH who was already on treatment.

CONCLUSION

The rate of malignancy in thyroid nodules with indeterminate cytology was 22.4%. Hard nodule consistency on physical examination was found to be associated with an increased risk of thyroid malignancy. The 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 in differentiating between hurthle cell and follicular neoplasms. The routine use of ultrasound for the evaluation of thyroid nodules with cytological diagnosis of follicular or hurthle cell neoplasms in Ethiopian hospitals is low.

Operational definition

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

The size of the nodule: It was described in centimters measured along its largest dimension.

Duration of symptoms: It described in years. When a patient's complaint was less than a year, it is stated infractions.

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

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

Intraoperative evidence of malignancy: Intraopertive features include 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

DECLARATIONS

Availability of data and materials

A soft copy of all data used for this article are available at the corresponding author, it can be made acquired at a reasonable request.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The study complied with the Declaration of Helsinki and was approved by the Research & Ethical committee of the department of surgery College of health science, Addis Ababa University.

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