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Malignancy Rates of Thyroid Cytology: Cyst Fluid Benign or Non-Diagnostic?

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: We sought to investigate subgroup distribution using Bethesda classification and risks for malignancy. We also compared the malignancy risk of cases that were denoted as non-diagnostic due to cystic contents, with cases that were denoted as non-diagnostic due to presence of other features.

Material/Methods: The study included pathology test results of 1,440 thyroid nodule samples diagnosed using Bethesda classification. Results of 305 thyroidectomy excision specimens from these patients were also compared with cytology results to determine the frequency of malignancy. The non-diagnostic group was divided into two categories: those with cystic contents, and others. Malignancy rates were separately calculated for the two groups, and compared with the other classification groups.

Results: Distribution of malignancy rates by Bethesda classification were as follows: non-diagnostic 12.5% (6/48), benign 1.5% (3/198), atypia of undetermined significance/follicular lesion of undetermined significance (AFLUS) 9% (1/11), suspicious for follicular neoplasm (SFN) 37.5% (3/8), suspicious malignancy 70% (8/26), malignancy 100% (14/14).

Conclusions: Despite the limited number of cases, our study concluded that cystic content was closer to the benign category than the non-diagnostic category if the assessment was based on malignancy rates. In this group, similar to aspirations containing plenty of lymphocytes that indicates colloid or lymphocytic thyroiditis, it is still controversial whether criterion for adequacy of follicular epithelial cells should be sought, or if they should be regarded as benign in order to prevent unnecessarily performance of repeat aspirations.

MeSH Keywords: Biopsy, Fine-Needle • Cyst Fluid • Thyroid Neoplasms • Thyroid Nodule

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Background

Fine needle aspiration cytology (FNAC) is the first-line diagnostic test for evaluation thyroid nodules [1]. It is a simple, rapid, and cost effective test that can effectively distinguish between neoplastic and non-neoplastic lesions of the thyroid.

In the past, in many cases, ambiguity, lack of standardization, and the failure of the treating physician to interpret cytological findings led to confusion and frustration in the sharing of clinically meaningful data between physicians, and even between and within institutions, as the terminology tended to differ from one pathologist to another and between different laboratories [2,3]. In 2007, a conference was held in Bethesda, MD, USA, with one of the objectives being to standardize the diagnostic terminology for the reporting of thyroid cytopathology results. The recommendations that resulted from this conference led to the formation of The Bethesda System for Reporting Thyroid Cytopathology. This classification scheme standardized thyroid-reporting cytopathology [2–4]. The Bethesda system describes six diagnostic categories of lesions: non-diagnostic, benign, atypia of undetermined significance/follicular lesion of undetermined significance, follicular neoplasm/suspicious for follicular neoplasm, suspicious for malignancy, and malignant [2–4]. The six diagnostic categories of the Bethesda system have individual implied risks of malignancy that influence management paradigms, and which also reflect literature reviews and institutional studies [2,4–8].

A smear is categorized as non-diagnostic if it does not fulfill the adequacy criteria of the Bethesda system [2,4,9]. For a solid nodule, a specimen is considered adequate if it contains at least six well-preserved and well-stained follicular groups, containing at least 10 cells. Thyroid cysts containing histiocytes but with little or no follicular cells are interpreted as non-diagnostic. In contrast, abundant thick colloid, as found in a colloid nodule, does not have a requirement for a minimum number of follicular cells.

In the present study, we sought to investigate the subgroup distribution using Bethesda classification and risks for malignancy in samples taken from 1,440 thyroid nodules diagnosed in our institution. We also compared the malignancy risks of cases that were denoted as non-diagnostic if they had cystic contents with those that were denoted as non-diagnostic due to the presence of other features.

Material and Methods

This retrospective study was done at Hitit University School of Medicine, Erol Olçok Training and Research Hospital, Turkey.

The study included pathology test results of 1,440 thyroid nodule samples diagnosed using the Bethesda classification between January 1, 2011 and May 15, 2013. The samples were taken from a total of 1,399 patients. Results of 305 thyroidectomy excision specimens were also compared with cytology results to determine the frequency of malignancy.

Bethesda classification was used for diagnosis [2,4]. If there was more than one aspiration specimen taken from the same nodule, and one specimen was considered non-diagnostic or benign, then that case was considered to be in the benign/non-diagnostic group.

All aspirations were performed under ultrasound guidance. Prepared smears were stained with MGG and samples fixed with alcohol were stained with PAP.

A total 305 thyroidectomy samples that were collected from patients operated in our institution were included in this study. Samples that we incidentally diagnosed as malignancy were excluded; and we assessed only those that had aspiration specimens from nodules.

The non-diagnostic group was divided into the cystic contents group and the others group. Malignancy rates were separately calculated for two groups and compared with the other groups.

Statistical analysis

All statistical analyses were performed using SPSS 21.0 (Licensed to Hitit University) statistical software. Continuous variables were expressed as mean ± standard deviation. Categorical variables were compared using chi-square test and Fisher's exact test as appropriate. Continuous variables were compared using independent samples *t*-test or Mann-Whitney U test. A p value <0.05 was considered statistically significant.

Results

We assessed results of 1,440 FNA samples taken from thyroid nodules of 1,399 patients. Out of these, 355 (22.6%) were diagnosed as non-diagnostic, 984 (68.3%) were diagnosed as benign, 53 (3.7%) were diagnosed as atypia of undetermined significance/follicular lesion of undetermined significance (AFLUS), 17 (1.2%) were diagnosed as suspicious for follicular neoplasm (SFN), 39 (2.7%) were diagnosed as suspicious for malignancy (SM) and 22 (1.5%) were diagnosed as malignancy (Table 1).

Out of 1,399 patients, 305 patients underwent operations in our hospital. Forty-five (14.7%) of these patients were diagnosed as malignancy and 260 of these patients (85.3%) were diagnosed as benign. Distribution of malignancy rates by

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Table 1. Frequency of cytological diagnoses (n: 1440).

Diagnostic category	Number of cases. (%)
Nondiagnostic	355 (22.6%)
Benign	984 (68.3%)
Atypical follicular lesion of undetermined significance	53 (3.7%)
"Suspicious" for follicular neoplasm	17 (1.2%)
Suspicious for malignancy	39 (2.7%)
Malignant	22 (1.5%)
Total	1440 (100%)

Table 2. Malignancy rates in thyroidectomy materials according to the Bethesda Classification.

Diagnostic category	Number of cases. (%)	Malignancy numbers and rates
Nondiagnostic	48 (15.8%)	6 (12.5%)
Benign	198 (65%)	3 (1.5%)
AFLUS	11 (3.6%)	1 (9%)
SFN	8 (2.6%)	3 (37.5%)
SM	26 (8.5%)	18 (70%)
Malignant	14 (4.5%)	14 (100%)
Total	305 (100%)	45 (14.7%)

AFLUS – atypia of undetermined significance/follicular lesion of undetermined significance; SFN – suspicious for follicular neoplasm; SM – suspicious for malignancy.

Bethesda classification was as follows: non-diagnostic 12.5% (6/48), benign 1.5% (3/198), AFLUS 9% (1/11), SFN 37.5% (3/8), suspicious malignancy 70% (8/26), and malignancy 100% (14/14) (Table 2).

Histopathological diagnoses of 198 nodules obtained from patients undergoing operations and diagnosed as benign according to the Bethesda classification were as follows: 195 were benign (160 were colloidal nodule/hyperplasia, 36 were chronic lymphocytic thyroiditis, two were granulomatous thyroiditis), three were malignancy (two were papillary thyroid carcinoma, and one were medullary carcinoma). Histopathological diagnoses of 48 nodules that were diagnosed as non-diagnostic were as follows: 42 were benign (38 were colloidal nodule/hyperplasia, four were chronic lymphocytic thyroiditis), six were malignancy (all were papillary thyroid carcinoma). Histopathological diagnoses of 11 patients that were diagnosed as AFLUS were as follows: 10 were benign (five were chronic lymphocytic thyroiditis and five were colloidal nodule/hyperplasia) and one was malignancy (papillary thyroid carcinoma). Histopathological diagnoses of eight patients that were diagnosed as SFN were as follows: five were benign (colloidal nodule/hyperplasia), three were malignancy (one was follicular carcinoma, one was well-differentiated thyroid tumor of uncertain malignant potential, and one was follicular variant of papillary thyroid carcinoma). Histopathological diagnoses of 26 patients that were diagnosed as SM were as follows: eight were benign (five were colloidal nodule/hyperplasia, three were chronic lymphocytic thyroiditis), 18 were malignant (all were papillary thyroid carcinoma) (Table 3).

Table 3. Histopathological diagnosis in resection materials according to the Bethesda category.

Diagnostic Category	Histopathological diagnosis and numbers
Benign	Papillary Thyroid carcinoma(2), Medullary Carcinoma (1)
Nondiagnostic	Papillary Thyroid carcinoma (6)
AFLUS	Papillary Thyroid carcinoma (1)
SFN	Papillary Thyroid carcinoma (1), Well-differentiated thyroid tumor of uncertain malignant potential (1), Follicular carcinoma (1)
SM	Papillary Thyroid carcinoma (18)
Malign	Papillary Thyroid carcinoma (14)

AFLUS – atypia of undetermined significance/follicular lesion of undetermined significance; SFN – suspicious for follicular neoplasm; SM – suspicious for malignancy.

Fourteen out of 48 patients undergoing operations were diagnosed as having non-diagnostic cystic content since the samples contained cystic content and did not contain sufficient follicular epithelial cells. Thirty-four patients were considered as non-diagnostic due to other causes (insufficient thyroid follicular epithelial cells, disturbed visibility due to intensive bleeding, etc.). Malignancy was not detected in any one of the materials taken from 14 patients that were diagnosed as having cystic content (0%). Malignancy was detected in six out of 34 other patients (17.6%) (Table 4). Malignancy rates were significantly lower in cases diagnosed as benign, than in those diagnosed as non-diagnostic (including non-diagnostic, cystic content, and other).

Discussion

In the present study, we retrospectively evaluated the thyroid FNA specimens that were diagnosed according to the Bethesda

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Table 4. Malignancy rates in cases diagnosed as benign and non-diagnostic.

Diagnostic category	Malignancy rate (%)	
Benign	3/198	(1.5%)
Cystic content	0/14	(0%)
Non-diagnostic (others)	6/34	(17.6%)
Non-diagnostic (Cystic content + others)	6/48	(12.5%)

Intergroup comparison	Rates	p value
Non diagnostic (cystic content + others) *vs.* benign	6/48 (12.5%) vs. 3/198 (1.5%)	0.002
Non diagnostic, cystic content *vs.* non diagnostic other	0/14 (0%) vs. 6/34 (17.6%)	0.161
Non diagnostic, other *vs.* benign	6/34 (17.6) vs. 3/198 (1.5%)	0.001
Non diagnostic, cystic content *vs.* benign	0/14 (0%) vs. 3/198 (1.5%)	1.000

classification between 2013–2016 in the Pathology Department of Hitit University Erol Olçok Training and Research Hospital. Although thyroid FNA has high specificity for benign and malignant lesions, the specificity shows a wide variability among different clinics. In previous studies on thyroid FNA, the frequencies showed a wide range as follows: benign ranged from 40% to 70%, non-diagnostic ranged from 2% to 23%, AFLUS ranged from 3% to 27%, SFN ranged from 1.2% to 25%, SM ranged 1.4% to 6.3%, and malignancy ranged from 2% to 16% [6–21]. The most important reason for this wide variability is likely due to the individual experience of the physicians that perform the aspirations and examine the specimens.

In this study, the diagnosis of benign specimen (68.3%) was higher than reported in the literature [6–16]. Bongiovanni et al. found in their series of 25,445 cases that the rate was 59.3% [22]. The main reason for this difference might be that in our institution, all nodules larger than 1 cm in diameter are routinely aspirated, even if the nodules are not considered suspicious based on clinical and ultrasound findings; thus, the rate of benign lesions might be higher.

The rate of non-diagnostic specimens was found to be 22.6% in our study. This is higher than what has been reported in the literature [6–15,19,20,22]. Reasons for this difference might include that the daily number of patients per physician was higher in our hospital, physicians who perform aspirations in our hospital were allowed an average of four minutes for each patient and the aspirations were performed using a single needle.

In our study, the total number of benign and non-diagnostic categories accounted for 90.9% of cases. In the literature the rate has been reported to range from 59% to 84% [6–20,23]. Bongiovanni et al. found in their meta-analysis that this rate was about 72% [22]. Since rates of these two categories were high in our study, the rates of other categories (AFLUS; SFN; SM; malignancy) remained relatively low.

The rate of AFLUS ranges from 3% to 27% in the literature [6–10,12–15,17–20,22,23]. In our clinic, the rate was found to be 3.7%. According to data from experienced clinics, the AFLUS rate should remain below 7%, and this category could be regarded as a "waste basket" [4]. From this point of view, the rate we found seems quite reasonable.

In the present study, SFN was found to be 1.2%, SM to be%2.7, and malignancy to be 2.5%. These rates were lower than rates previously reported in the literature [6–16,22]. The reason for this difference is likely the higher rate of our cases in the benign and non-diagnostic category.

In our study, 45 out of 305 patients (14.7%) who underwent an operation were diagnosed with malignancy. Malignancy rates in similar studies ranged from 20% to 53% [8–13,16]. The main reason for lower rates in our study was thought to be because patients who were diagnosed with malignancy via thyroid FNA tended to be admitted to higher volume centers for their operation.

In our study, 198 out of 305 patients (65%) who underwent an operation were diagnosed with benign lesions via thyroid FNA and they were operated on for other clinical indications. Only three of these patients (1.5%) had a diagnosis of malignancy. This rate was compatible with the literature [2,4–16,18,22,23]. Ali et al. suggested in their study that this rate should remain between 0% and 3% [4]. In our study, three patients who had been misdiagnosed were diagnosed with papillary thyroid carcinoma (two patients) and medullary carcinoma (one patient) by histopathological examination of the thyroidectomy specimen (Table 3).

In this study, 48 out of 305 patients (15.8%) who underwent an operation were diagnosed as non-diagnostic, and of these, six patients (12.5%) were diagnosed as having malignancy (papillary thyroid carcinoma) by histopathological examination of

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thyroidectomy specimens (Table 3). Ali suggested that this rate should remain between 1% to 4% [4]. According to the Bethesda classification algorithm, patients who are diagnosed as non-diagnostic should receive a repeated aspiration after a reasonable period of time. If the aspiration is still non-diagnostic and there is high clinical suspicion, the patient should have the operation [4]. However, in our study, patients diagnosed as non-diagnostic based on the first aspiration had the operation without performing a second aspiration and thus, our malignancy rates were found to be higher than the rate reported in the literature.

In a recent study, the malignancy rates for patients who were diagnosed as SFN, SM, and malignancy were 37.3% (3/8), 70% (18/26), and 100% (14/14), respectively (Table 2). These rates are similar with those reported in the literature and those recommended by the Bethesda classification [4–16,22].

According to the Bethesda classification, if aspiration specimens that contain cystic content (macrophages, cyst fluid, etc.) do not contain sufficient follicular epithelial cells, then they should be regarded as non-diagnostic since cystic papillary thyroid carcinoma cannot be excluded; and it is also recommended that they should be reported as "non-diagnostic cystic content". In this situation, the decision is left to the clinician's discretion; a second aspiration is recommended if ultrasound findings are suspicious, whereas if there is no suspicion on ultrasound it may be considered a benign finding [2,4]. Garcia et al. compared malignancy rates in thyroid FNA specimens between patients who were diagnosed as non-diagnostic due to cystic content and those who were diagnosed as non-diagnostic due to other causes. Malignancy rates in specimens with cystic content was 14.3%, whereas it was 6.6% in the other group [24]. In another study by Yoon et al., nodules obtained from a total of 393 thyroidectomy samples were divided into three categories as solid, mainly solid, and mainly cystic. Malignancy rates of these groups were found to be 29.2%, 16.7%, and 9.5%, respectively [25]. In our study, there was no malignancy in patients who were diagnosed as non-diagnostic due cystic content (0/14), whereas six out of 34 patients (17.6%) who were diagnosed as non-diagnostic had malignancy (Table 4).

Conclusions

Despite the limited number of cases, our study concluded that cystic content was closer to the benign category than to the non-diagnostic category if the assessment was based on malignancy rates. In this group, similar to aspirations containing plenty of lymphocytes that indicate colloid or lymphocytic thyroiditis, it is still controversial whether criterion for adequacy of follicular epithelial cells should be sought, or if they should be regarded as benign in order to prevent unnecessarily performed repeat aspirations.

Conflict of interest

None.

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