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Research Article

Ultrasound-Guided Fine-needle Aspiration of the Thyroid in Cytology Practice

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Abstract

Background: Fine-needle aspiration (FNA) of the thyroid gland is a widely accepted and accurate method for triaging patients with thyroid nodules. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is used to standardize terminology and convey the risk of malignancy.

Objective: The aim of the study is to analyze the benefit of ultrasound in our daily cytology practice and the utility of the TBSRTC to predict the malignancy risk. We correlated cytology and ultrasound findings with histology reports.

Methods: Data on patient cytology were retrieved by a retrospective search of all thyroid fine needle aspiration cytology (FNAC) reports issued at the Department of Cytopathology, Söder Hospital, Karolinska University from January 2012 to June 2013. A total of 619 specimens were reclassified according to the TBSRTC. When applicable the cytological diagnosis was compared with follow-up cytology and/or the histology report.

Results: Cytology results were nondiagnostic in 24 (3.87%) nodules, benign in 553 (89,33%), atypia of undetermined significance or follicular lesion of undetermined significance,6 (1 %), follicular neoplasm or suspicious for a follicular neoplasm 14 (2.26 %), suspicious for malignancy,5 (0.8%), and malignant in 17 cases (2,7 % of the lesions).FNA showed a sensitivity of 84.62%, a specificity of 99.33 %, with prevalence of a malignant disease in 4.15 %.Ultrasonography proved to be very useful in our daily cytology practice in order to achieve representative samples. A representative specimen was obtained in 95% of patients examined by ultrasound. When ultrasound was not used, only 87 % of the patients presented a representative cell sample. Papillary thyroid cancer accounted for 65% of the cancers, followed by follicular neoplasm (25%), anaplastic carcinoma (5%), and metastatic renal cancer (5%).

Conclusion: Ultrasound is an important diagnostic modality for the evaluation of thyroid lesions, providing crucial information about the nature of the lesion. Its use in cytology practice increases the chance of obtaining an adequate cytological specimen, reaching a correct diagnosis, and avoiding unnecessary surgery. This study also demonstrates that the ultrasound can be handled by the cytologist him/herself, which has obvious practical advantages.

INTRODUCTION

Ultrasonography has been used in recent clinical studies to assess thyroid size, vascularization, and calcifications, which has led to higher estimates of goiter prevalence than those of studies in which goiter was assessed by physical examination alone. This method is highly accurate in determining whether a lump is malignant (cancerous) or benign [1-3,5].

FNAC is the gold standard in the examination of thyroid nodules. Latest studies imply a high sensitivity and specificity for predicting thyroid malignancies averaging 83% [6] and 92% respectively [7]. However; FNAC has limitations and a false-negative rate of approximately 5% [6] in one study and in others between 0-29% [8]. In contrast the false-positive rate for a cytology reading of suspicious of malignancy or malignancy has been reported before in other series with about 10% [9].

Real-time ultrasound allows for continuous visualization of the needle during insertion and sampling, thus minimizing the risk of false-negative results. Historically, ultrasound guided-

FNA (US-FNA) has been always performed by a radiologist in a designated radiology suite. With the development of smaller and more portable ultrasound machines, wireless, there has been a push for clinicians other than radiologists to perform this procedure [3-5].

During the last 6 years, US-FNA cytology has been performed at our institution in the Cytology Department in almost all patients with thyroid nodules. US-FNA of the thyroid can be done on an outpatient basis. It is a relatively painless and minimally invasive method that does not require local or general anesthesia. Recovery time is short, and a hospital stay is normally not required.

The objective of this retrospective study was to analyze the benefit of ultrasound of the thyroid in daily cytology practice, which allows for the simultaneous evaluation of clinical, macro-morphological (ultrasound image), and micro-morphological (cytology) parameters to predict the risk of malignancy, as ultimately demonstrated in the histological specimens [1-5].

Early studies demonstrated the value of ultrasound, but correlation with histology was not always available [3,5]. This information is included in our study.

MATERIALS AND METHODS

Data on patient cytology were retrieved by a retrospective search of all thyroid FNA cytology reports that were issued in the Department of Cytopathology at Söder Hospital, Karolinska Laboratory in Stockholm between January 2012 and June 2013. A total of 619 thyroid FNA cytology diagnoses were reclassified according to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) [10].

FNA

FNA was performed with a 0,4mm, sometimes a 0,6mm, and occasionally a 0,7mm in diameter needle using the capillary method or vacuum-assisted method and usually guided by ultrasound [5]. The ultrasound guided FNAs were done and the smears were analyzed, by an experienced cytologist (Dr. A. Herder). When a surgery decision was taken a second opinion diagnosis was made by cytologists in another hospital (Karolinska Solna). In all cases, air-dried Giemsa-stained smears were evaluated, and sometimes the Papanicolaou staining was performed. The reclassified cytology results were subcategorized as unsatisfactory, benign, atypia of undetermined significance or follicular Lesion of undetermined significance, follicular

Table 1: Risk of malignancy and recommended clinical management.

	TBSRTC: Recommended Diagnostic Categories	Risk of Malignancy (%)	Usual Management
Number	**Name of the Category**		
I	**Non Diagnostic of Unsatisfactory**	1-4	Repeat FNA with ultrasound guidance
	Cystic fluid only		
	Virtually acellular specimen		
	Other (obscuring blood, collecting artifacts, etc)		
II	**Benign**	0-3	Clinical follow-up
	Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc)		
	Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical content		
	Consistent with granulomatous (subacute) thyroiditis		
	Other		
III	**Atypia of undetermined significance or follicular lesion of undetermined significance**	5-15	Repeat FNA
IV	**Follicular neoplasm or suspicious for follicular neoplasm**	15-30	Surgical lobectomy
V	**Suspicious for Malignancy**	60-75	Near total thyroidectomy or surgical lobectomy
	Suspicious for papillary carcinoma		
	Suspicious for medullary carcinoma		
	Suspicious for metastatic carcinoma		
	Suspicious for lymphoma		
	Other		
VI	**Malignant**	97-99	Near-total thyroidectomy
	Papillary thyroid carcinoma		
	Poorly differentiated carcinoma		
	Medullary thyroid carcinoma		
	Undifferentiated (anaplastic) carcinoma		
	Squamous cell carcinoma		
	Carcinoma with mixed features (specify)		
	Metastatic carcinoma		
	Non-Hodgkin's lymphoma		
	Other		

neoplasm, suspicious for malignancy, or positive for malignancy (Table 1).

Ultrasonography

Most patients (95%) were evaluated by ultrasound previous to FNA, and the images were archived. The FNAs were subsequently guided by real time ultrasound - all in the same session. A small number of cases (5%) underwent FNA with palpation guidance alone.

The cytology doctor performed ultrasound with a linear multi frequency transducer of 14 MHz for morphological analysis (B-mode) and for power Doppler evaluation.

In some patients, the referred nodule was not obvious by palpation, and sampling for cytology was performed solely on the basis of the ultrasonographic image. Often, the cytological work-up included sampling from the other lobe and/or nodules other than the palpable one. Routinely, the thyroid was also ultrasonographically scanned and, if suspicious, sampled in the case of cystic, non-squamous (determined by quick-stain) metastases in the neck.

Solid or predominantly solid nodules with the following features were defined as "suspicious" by ultrasound: marked hypoechogenicity (compared with the adjacent strap muscle); calcifications (especially if irregular); hypoechogenicity combined with microlobulation, irregular margins, or a taller-than-wide shape (greater in the anteroposterior dimension than in the transverse dimension); or predominantly or exclusively central vascularization. These definitions have been used in other institutions [3,5]. Clinical data were recorded and correlated with the cytological findings. The results of FNA cytology were compared to the corresponding histological diagnoses whenever surgery had been performed.

Malignancy evaluation according to ultrasound findings

The imaging characteristics of a mass (nodule type, site, margins, microcalcifications, macrocalcifications, echogenicity, size, vascularity) were identified at examination followed by FNA.

Criteria for malignancy according to cytology findings

The recommended diagnostic categories by TBSRTC, risk of malignancy and recommended clinical management are seen in Table (1).

Cytological criteria for papillary thyroid carcinoma were ultimately defined by nuclear cell characteristics as follows: A relatively large nuclear size, round to slightly oval nuclear shape, hypodense chromatin, intranuclear cytoplasmic inclusions (ground glass nuclei), nuclear overlapping, and nuclear grooves.

Comparison with histology

Histological outcomes were obtained from the pathology database.

Statistical analysis

Quantitative data were summarized and expressed as percent, whereas qualitative data were expressed with the number of cases. Groups included in the study were compared using the Pearson correlation test. Sensitivity and specificity were calculated. Significance was set at the value of less than 0.05 level.

RESULTS AND DISCUSSION

The most common thyroid disease in the community is simple physiological goiter but several studies show that the incidence of thyroid cancer is increasing widely [11-16]. This increase of malignancy cannot be satisfactorily explained as an artifact of changes in classification systems and likely reflects a real increase in incidence. Fine-needle aspiration (FNA) cytology has proven to be an important and widely accepted cost-effective, simple, and minimally invasive procedure for triaging patients with thyroid nodules. FNA cytology findings play a vital role in selecting patients for surgery.

Adequacy of cytology specimens

We obtained a diagnostic cell sample in practically all patients where the FNA was ultrasound-assisted. In the cases where sampling was done by physical examination alone the adequacy of the material was less, about 87.6%.

Complications during sampling are possible, like pain and hematoma but in the cases reviewed, no significant complications occurred. One explanation is the small size diameter needles used (0,4 mm, 0.6 mm, occasionally 0.7 mm). US-FNA also tends to ensure diagnostic cell material with fewer needle passes than the traditional palpation guided technique [17].

Cytology and classification according to the TBSRTC

The TBSRTC was used in all patients following Bethesda criteria (Table 1), and the results are presented in Tables (2) and (3). As in many other studies, the most common diagnosis was nodular goiter, followed by Hashimoto thyroiditis and hyperplasia classified as TBSRTC category II. Most of the patients were women with benign or malignant nodules, which is consistent with the results of other studies [18-20]. The diagnosis of TBSRTC category III in patients with an apparent mass was an important criterion for selecting patients for follow-up (Table 1,3). Five of the patients in the study were classified as Bethesda III, and were followed with a second cytological investigation, together with 109 other patients selected for follow up due to clinical considerations. Of these altogether 114 patients, 83 were diagnosed with nodular goiter in both the primary, and the secondary cytological investigation. 13 cases with Bethesda II (colloid goiter) were operated, and the histological diagnosis was also colloid goiter as showed in Table (3). Seven cases with Bethesda II (Lymphocytic thyroiditis) were followed, and 6 of these kept the same cytological diagnosis. In one case the follow up upgraded the diagnosis to a Bethesda IV and histology showed follicular neoplasm, Table (4).

One case with a follicular neoplasm (Bethesda IV) in the initial cytology showed papillary thyroid carcinoma in the second cytology, as well as in the subsequent histology (Table 4). The ultrasound showed Microcalcifications and rich vascularization, both, which are indicators of malignancy. The initial FNA was guided by palpation, but in the follow up ultrasound was used (Table 5).

Table 2: The figure illustrates the age, gender and diagnoses according to Bethesda classification.

Diagnosis	Number of Patients	Age range, years	Female	Male
Nondiagnostic or unsatisfactory	24	42-75	20	4
Benign	553	13-87	482	71
Atypia of undetermined significance or follicular lesion	6	35-83	4	2
Follicular neoplasmn or suspicious	14	22-66	12	2
Suspicious for Malignancy	5	38-39	3	2
Malignant	17	36-87	16	1
Total	619	13-87	537	82

Table 3: Bethesda classification, cytology findings, follow up and final histology is showed in 27 cases with Bethesda II-IV in which surgery was performed as illustrated.

Cases	Bethesda	Cytology diagnosis	Follow up	Final histology
1	II	Colloid goiter		Colloid goiter
2	II	Colloid goiter	Colloid goiter	Colloid goiter
3	II	Colloid goiter		Colloid goiter
4	II	Colloid goiter	Colloid goiter	Colloid goiter
5	II	Colloid goiter		Colloid goiter
6	II	Colloid goiter		Colloid goiter
7	II	Colloid goiter	Colloid goiter	Colloid goiter
8	II	Colloid goiter		Follicular thyroid adenoma
9	II	Colloid goiter		Oxyfilt thyroid adenoma and colloid goiter
10	II	Colloid goiter		Colloid goiter
11	II	Colloid goiter		Colloid goiter
12	II	Lymphocytic thyroiditis	Lymphocytic thyroiditis	Lymphocitic thyroiditis
13	III	Suspect adenoma		Lymphocitic thyroiditis
14	IV	Follicular neoplasm (oncocytic type)	Hurtlel cell adenoma	Hurtlel cell adenoma
15	IV	Follicular neoplasm (oncocytic type)	Goiter (hyperplastic process)	Hurtlel cell adenoma
16	IV	Follicular neoplasm (oncocytic type)		Lymphocitic thyroiditis
17	IV	Follicular thyroiditis and lymphome		Oxyfilt thyroid adenoma, colloid goiter and Lymphoma
18	IV	Follicular neoplasm (oncocytic type)		Colloid goiter and Oxyfilt metaplasia
19	IV	Follicular neoplasm (oncocytic type)	Hurtlel cell adenoma	Hurtlel cell adenoma
20	IV	Follicular neoplasm (oncocytic type)		Hurtlel cell adenoma
21	IV	Follicular neoplasm (oncocytic type)		Hurtlel cell adenoma
22	IV	Follicular neoplasm (oncocytic type)	Follicular neoplasia	Follicular thyroid adenoma
23	IV	Follicular neoplasm (oncocytic type)		Hurtlel cell adenoma
24	IV	Follicular neoplasm (oncocytic type)		Follicular type with colloid goiter
25	IV	Follicular neoplasm (oncocytic type)	Follicular neoplasia	Follicular adenoma
26	IV	Follicular neoplasm (oncocytic type)		Hurtlel cell adenoma
27	IV	Follicular neoplasm (oncocytic type)		Hurtlel cell adenoma

Table 4. The table illustrated cases with initial cytology and follow up and the cases that were upgraded.

Initial Cytology/Follow Up	Diagnosis	N
Initial cytology	Colloid goiter	13
Follow Up	Colloid goiter	13
Initial cytology	Lymphocityc thyroidit	7
Follow Up	Lymphocityc thyroidit	6
	Follicular neoplasm	1
Initial cytology	Follicular neoplasm	1
Follow Up and histology	Papillar thyroid carcinoma and follicular cancer	1

The unexpectedly low rate of Bethesda III and IV cases in our study could be due to the use of ultrasound, which enhances cytology accuracy. The local tradition is also to do a repeat cytology if the first one is inadequate. An additional factor is perhaps the long experience of the examining cytologist (30 yrs). Finally the retrospective reclassification might have resulted in a skewed Bethesda grouping.

Correlation with histology

Histology is the best technique for final tumor classification; the relationship between cytology and histology results is presented in Tables (3,6). The patient age-span was 37 to 91 yrs, and 90% of the patients were women. In our study, the results of US-FNA cytology and histology in the malignant cases were correlated as seen in Table (6).

Three patients showed Bethesda V and 14 Bethesda VI.

These 17 cases were confirmed as malignant histologically (Table 6). The most common malignant lesion was papillary carcinoma, but anaplastic cancer and metastatic renal clear cell carcinoma was also found. There were no medullary carcinomas among the malignancies, which is however an uncommon tumor that accounts for 3-4% of all thyroid neoplasias. Both cytologically and histologically this neuroendocrine (calcitonin) neoplasm is a spindle and epitheloid cell tumour often containing amyloid, and in the cytological smears rather frequently displaying neuroendocrine granules. Except for a malignant lymphoma neither does this tumour series contain any small cell malignancies [21].

Correlation with ultrasound findings

Ultrasound findings are presented in Table (7). We found a good correlation between the tumour size as measured by ultrasound and the size in the histological specimen (Pearson correlation test with r=0,96).

Papillary thyroid carcinoma has a predilection for women as others have shown, and this is also the case in our study [18-20]. The diagnosis of thyroid cancer by US-FNA cytology correlated with suspicious ultrasound findings in 18 of 20 patients (90%). All lesions with Bethesda V and VI on FNA cytology were selected for surgery, and subsequently proved to be malignant.

In 55% of patients with malignancies, the tumor was located in the right side and had calcifications. Most tumors (70%) had irregular borders, and 50% were hypoechogenic, and 70% showed abnormal vascularization. Most (65%) of the malignant cases were diagnosed as papillary thyroid cancer.

Malignancy was associated with gender and sonographic features. The use of ultrasound evaluation of thyroid nodules increased the quality of the cytology specimen and provided important diagnostic information (Table 7), (Figure 1) [1-3]. Irregular borders, abnormal vascularization, and hypoechogenicity were the most common ultrasound features present in the patients with cancer.

The success of US-FNA in accurately detecting neoplastic changes in the thyroid on initial examination of patients with a palpable mass depends on several factors such as operator

Table 5: Ultrasound Findings.

Cases	Ultrasound Findings	FNA	Clinical Follow Up
1	Microcalcifications, hipoechogenic	Suspect follicular neoplasm	Lymphocytthyroiditic
2	Microcalcifications, hypoechogenic, abnormal vascularization	Suspect follicular neoplasm	Papillar thyroid cancer and follicular cancer

Table 6: Cytology and histology findings of patients with malignant thyroid nodules, W: woman; M: male.

Case	Age, years	Sex	Cytology	Histology	Metastasis	Size ultrasound (mm)	Size histology (mm)
1	37	W	Papillar thyroid cancer	Papillar thyroid cancer	0 of 10	10	8
2	83	W	Papillar thyroid cancer	Multifocal Hurtlel cell cancer	3 of 6	10	9
3	47	W	Papillar thyroid cancer	Papillar thyroid cancer	11 of 14	20	14
4	91	W	Anaplastic thyroid carcinoma	Papillar thyroid cancer	-	40 x 50	43 x 26
5	39	W	Suspect thyroid cancer	Papillar thyroid cancer	14 of 15	-	19 x 10
6	53	W	Suspect thyroid cancer	Papillar thyroid cancer	0 of 1	15	22
7	67	W	Metastasis renal carcinoma	No surgery was performed	-	-	-
8	45	W	Papillar thyroid cancer	Papillar thyroid cancer	1 of 7	6	6
9	66	W	Follicular neoplasia with oncocytic metaplasia	Follicular cancer	0 of 1	-	46
10	42	W	Papillar thyroid cancer	Multifocal thyroid cancer	11 of 14	20	18
11	59	W	Papillar thyroid cancer	Micropapillar thyroid cancer	4 of 30	40	44
12	38	W	Suspect thyroid cancer	Papillar thyroid cancer and follicular cancer	-	-	-
13	38	W	Papillar thyroid cancer	Papillar thyroid cancer	-	15	15
14	55	W	Papillar thyroid cancer	Micropapillar thyroid cancer	0 of 13	10	8
15	46	W	Papillar thyroid cancer	Micropapillar thyroid cancer	0 of 16	9	10
16	46	W	Papillar thyroid cancer	Papillar thyroid cancer	7 of 33	5	5 and 2
17	39	M	Papillar thyroid cancer	Papillar thyroid cancer	9 of 22	19 and 8	16 and 8

Table 7: Ultrasound findings in the 17 patients with malignant thyroid nodules. The table illustrates the localization of the nodule.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Site	R	R	R	L	R	R	R	L	L	R	R	L	I	R	L	R	I
Margins	R	I	I	I	R	R	I	I	I	I	R	R	I	I	I	I	I
Microcalcifications	Y	Y	Y	N	N	Y	Y	N	N	N	N	Y	Y	Y	N	Y	Y
Macrocalcifications																	
Irregular calcifications	N	Y	Y	N	Y	N	N	N	N	Y	N	N	Y	N	Y	Y	N
Hypoechogenic	Y	Y	N	Y	N	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y
Size (mm)	10	10	20	40X50	-	15	X	6	-	20	40	-	15	10	9	5	19
Abnormal vascularity	Y	N	N	Y	Y	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	Y

Abbreviations: R: Right, L: left; Margins: R: regulars, I: Irregulars; Microcalcifications; Hypoechogenic; Vascularity: Yes (Y): Present, Not (N): Not Present.

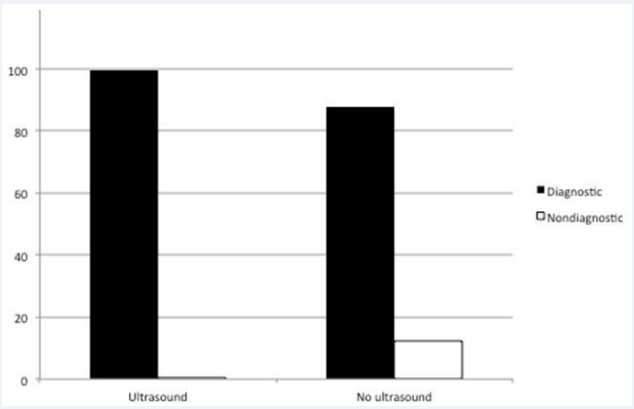

Figure 1 Cases that showed diagnostic material with ultrasound fine needle aspiration or without ultrasound.

experience and tumor appearance. The standard sonographic features used to predict the malignant status of thyroid nodules include irregular calcifications, increased vascularisation, hypoechogenic areas, and irregular borders. Even when all features are present, the diagnostic accuracy of ultrasound alone is about 90%. Conversely, only 75% of malignant thyroid nodules will demonstrate at least three ultrasound features of malignancy. When most criteria for malignancy are fulfilled in the ultrasound evaluation, the added benefit of performing US-FNA is clear. All patients with TBSRTC category V-VI tumors in our study fulfilled most of the ultrasonographic criteria of malignancy (Table 6).

There are operator-dependent factors, such as the ability to visualize and categorize thyroid nodules based on sonographic features, selection of suspicious nodules for aspiration, and skill in achieving diagnostic material. The contribution of immediate, preliminary, cytological assessment (microscope and a quick-stain in the room) in reducing the number of nondiagnostic cases is well established [5,17]. For a correct cytological diagnosis, in many cases, ultrasound guidence is mandatory.

Of great importance is, with the frequent use of ultrasound as described, that small, not palpable, and mostly papillary malignancies, other than the palpable lesion will be detected. In the present study this was the case in 2,74 % of the malignancies.

Training is needed to be able to perform an ultrasonographic examination, as well as the US-FNA, but this study, as others, shows that ultrasound is an invaluable tool in the daily cytology practice [5,17].

CONCLUSIONS

Ultrasound and fine needle aspiration cytology are important diagnostic modalities for the evaluation of thyroid lesions. These techniques can be used one by one, or together, enabling real time ultrasound needle guidance, thereby reducing the number of false negative results.

This study shows that both techniques, after some training, can be handled by the cytologist her/himself and thus minimizing the time lap between the primary medical examination, and the final diagnosis. In addition this approach reduces the number of patient health-care visits.

Compared to physical examination/palpation alone, ultrasound provides the cytologist with crucial diagnostic information, creating the basis for an optimal and precise diagnostic work. In the cytology suite, addition of ultrasound, and ultrasound guided FNAC, enables detection of malignancies other than the palpable nodule.

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