Journal of Thyroid Disorders & Therapy
ISSN: 2167-7948

Cohen et al., Thyroid Disorders Ther 2013, 2.2
DOI: 10.4172/2167-7948.1000129

Research Article Open Access

The Use of Surgeon Performed Ultrasound in the Assessment of Indeterminate Thyroid Nodules

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Abstract

Introduction: Indeterminate thyroid nodules (category 3 and 4 by the Bethesda System for Reporting Thyroid Cytopathology - BSRTC) hold a therapeutic dilemma. Our objective was to evaluate the clinical importance of surgeon performed ultrasound (SUS) in assessing thyroid lesions with BSRTC 3 and 4.

Materials and methods: All data of all patients referred for a thyroid nodule work-up, including SUS and FNA, between July 2010 and December 2012 was recorded. All patients were treated according to accepted clinical guidelines. 105 patients were diagnosed with indeterminate cytology. 43 patients were referred to surgery, and 62 were referred to further follow up. In this retrospective chart review, all clinical, sonographical, cytopathological and histopathlogical data in this group was analyzed. Patients were subdivided according to follow up and outcome. Correlation between ultrasound features and final pathology was analyzed.

Results: Malignancy rate was 35% (15/43) in the operated group, with 37% in BSRTC category 3 (10/27), and 31% of category 4 (5/16). Benign disease on histology or repeated cytology was found in 80% (40/50) of all *BSRTC 3,* and 72% (17/22) of 4. The presence of two or more known sonographic features to be associated with malignancy were significantly higher in the malignant group (43% vs. 23%, p=0.035).

Conclusions: SUS allows a better patient selection for non-surgical follow up, reducing unnecessary operations.

Keywords: Ultrasound; Thyroid nodule; Indeterminate; Surgeon performed; Sonographic features

Introduction

Thyroid nodules with indeterminate cytology hold a therapeutic dilemma for both surgeon and patient. It is a result of the inability to rule-out malignancy in a nodule which is most likely to be benign [1-13]. The definition of indeterminate cytology is a matter of controversy. The diagnostic category "Atypia of Unknown Significance (AUS)/Follicular Lesion of Unknown Significance (FLUS)" was proposed at the Bethesda conference [1] and though considered a consensus among pathologists and the National Cancer Institute (NCI), it is not accepted by all thyroid associations [4]. Some still include only "follicular neoplasm" or "indeterminate" and "suspicious for malignancy" categories.

The prevalence of indeterminate nodules differs between different reports and range between 15-30% [1,2,5]. The percentage of indeterminate nodules found to be malignant on biopsy differs for each classification and ranges about 10-25%, 25-30%, 60-75% for Atypia/Follicular lesion of undetermined significance (AUS/FLUS), Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/FNS) and Suspicious for Malignancy, respectively (Bethesda System for Reporting Thyroid Cytopathology (BSRTC) classes 3, 4,5 respectively) [1-3,9].

While an AUS/FLUS (BSRTC 3) result can be managed by repeated fine needle aspiration (FNA) and conservative approach [1], the standard management for FN/FNS (BSRTC 4) classification is thyroid lobectomy [1,5,14]. Assessing the risk of malignancy in different BSRTC 3 nodules determines which nodule should be surgically excised and which follicular lesion should be managed conservatively, decreasing possible complications and cost following surgery.

The clinical role of Ultrasound (US) in the assessment of the thyroid nodule has been widely accepted, and it is been used routinely in the management of thyroid nodules [3,15,16-18]. Despite known limitations such as being user-dependent, US provides valuable information about the nature of the node at diagnosis, trends and changes of the nodule throughout routine follow-up and additional valuable information such as lymph node involvement. Partly due to its inherent "user dependency" and technical advancements such as higher portability and better resolution, there is a shift towards the use of US by the surgeon rather than the radiologist, over the last years. In experienced hands, it is becoming part of the clinical examination, with major impact on patient selection for surgery and timing of surgery [8].

Different US characteristics of the thyroid nodule have been correlated with higher risk of malignancy, and were found to be a significant tool for assessing such risk [4,8,10,16-25]. These include irregular borders or poorly defined margins, hypoechoic echogenicity, presence of microcalcifications, solid structure, height greater than width and increased vascularity.

Different predictive models, based on clinical and sonographic scoring have been published in recent years [20,21,24], yet other publications did not find US findings to be of clinical value [9,13,26]. The Thyroid Imaging Reporting and Data System (TIRAD) [24], the most comprehensive model for risk stratification of thyroid malignancy based on sonographic features, was made in order to standardize thyroid imaging and improve communication between radiologists

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Received July 04, 2013; **Accepted** August 24, 2013; **Published** August 27, 2013

Citation: Cohen O, Yehuda M, Diment J, Lahav Y, Halperin D (2013) The Use of Surgeon Performed Ultrasound in the Assessment of Indeterminate Thyroid Nodules. Thyroid Disorders Ther 2: 129. doi:10.4172/2167-7948.1000129

and surgeons, following the same logic as BSRTC with pathologists [1].

Surgeon Performed US (SUS) has gained popularity in the past decade, yet studies of its clinical outcome benefit are limited [8,25,27]. None of these refers to the new Bethesda classification system [6].

The purpose of this study is to evaluate the clinical importance of SUS in assessing the risk of malignancy for Bethesda 3 and 4 categories.

Methods

In our academic center, all patients with suspected or proved morphological abnormalities of the thyroid, are evaluated in a dedicated thyroid clinic, with a comprehensive approach, by a head and neck surgeon (M.Y.) who is also qualified in cervical sonography and Ultrasound Guided FNA (USGFNA). During the first visit, the surgeon evaluates the patient and decides whether there is an indication for acquiring cytological information. If so, an FNA is performed by the surgeon, with an 'on-the-spot' adequacy evaluation by the surgeon or a cyto-screener. On the first follow up visit, the results and recommendations for further treatment are given. These are based on the widely accepted guidelines and in combination with clinical and sonographic experience and judgment of the surgeon. A joint patient-surgeon decision is made as to either go for surgery, or follow up in the clinic with repeated FNA, or discharge for community based follow up.

The medical records of all consecutive patients referred to the thyroid clinic in the department of Otolaryngology at Kaplan Medical Center between July 2010 and December 2012 were collected and recorded. Patients whose nodules were diagnosed as BSRTC category 3 (AUS/FLUS) or 4 (FN/SFN) following FNA were included in this research. Patients who met the inclusion criteria were further divided according to the chosen treatment: conservative follow up subgroup, including repeated FNA, and referral for surgery subgroup. History, relevant risk factors and TSH levels were documented in the patients' medical records. Physical examination findings, including numbers of nodules, palpability, consistency and location were documented in the patients' medical record as well. The clinical and sonographical data were recorded on a designated form. All the clinical data, as well as all diagnostic US and USGFNAs were performed in the outpatient thyroid unit clinic by a single surgeon. US was done with high resolution, portable 8-12 MHz system (Sonosite, M-Turbo, with 35mm linear array transducer).

Patient with suppressed TSH underwent thyroid isotope scan. Those with "warm" nodules were excluded from this study.

US characteristics included nodule's size, texture (solid\cystic\mixed), echogenicity (hypoechoic\isoechoic\hyperechoic), borders (regular\irregular), vascularity (intranodular\perilesional), and calcifications (micro\macro-calcifications). Additional features including spongiform lesion, depth larger than width and nodules with comet tail sign were all documented when present.

After each FNA puncture, at least one slide was assessed for adequacy immediately by the surgeon and\or a cytologist screener in situ, using dry smear Diff quick staining. The remaining slides were put in 96% alcohol for fixation and sent for Papanicolau staining. Dry and alcohol fixed smears were sent for final pathological examination by a dedicated cytopathologist (J.D.) in the Pathology Department at Kaplan Medical Center.

Cytological diagnostic criteria were based on the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) [1].

Specimens were defined as Atypia or Follicular Lesion of Unknown Significance (AUS/FLUS, BSRTC-3) when the findings were not convincingly benign but were not diagnostic of a neoplastic or malignant process. Several scenarios were included in this category, with prominent population of microfollicles but no other criteria for follicular neoplasm, or some cellular atypia being the most relevant for this study.

Follicular Neoplasm or Suspicious for Follicular Neoplasm category FN/ SFN, (BSRTC-4) included aspirates with high cellularity, scant colloid, overlapped nuclei, numerous microfollicles and no nuclear features of Papillary Thyroid Carcinoma (PTC).

Patients were managed according to clinical judgments of the surgeon (M.Y.) and the patient's will. Decision of lobectomy was made for patients with BSRTC category 3 and 4 according to clinical risk factors, physical findings, changes in nodule size, US features, and after discussing all treatment options with the patient. Patients who were followed conservatively, had follow up visits in the thyroid clinic every 6 months, and repeated USGFNA was held.

Surgery was performed by qualified head and neck surgeons in the Department of Otolaryngology in Kaplan Medical Center. Frozen sections were taken according to intra-operative judgment of the performing surgeon, in the absolute minority of the cases.

Histological examination and diagnosis was performed in the Pathology Department at Kaplan Medical Center by the same pathologist (J.D.). Histology result referred to the index nodule that was assessed clinically, sonographically and cytologically.

Statistical methods

Quantitative results are presented using their means ± SD. Qualitative results are presented using their percentage. In order to compare the results between the two groups, benign vs. malignant, we used the Chi square test for the categorical measurements and the t-test for independent groups for the quantitative measurements. The sensitivity, specificity, PPV, NPV and accuracy where also computed using 2 by 2 categorical tables. All computations were done using SPSS statistical software ver. 20.

Results

Of the 1239 Thyroid USGFNAs that were performed by the senior author (M.Y.) between July 2010 and December 2012 at Kaplan Medical Center, 105 (8.5%) were classified as Bethesda category 3 and 4 and were included in this study. Of the 105 nodules, 76 were diagnosed as AUS\FLUS (72%) and 29 as FN/SFN (28%). The majority of the patients were females (69%, 72/105). TSH levels were normal or higher in 101 patients (ranged 0.01-10.3 mg%, mean=2.23). 4 patients had TSH values below normal values, and were referred to a thyroid scan. In all 4 patients there was no correlation between suspected nodule and iodine uptake.

43 (41%) patients were operated. Of the operated patients, 27 were diagnosed with BSRTC 3 and 16 patients were diagnosed with BSRTC 4. In 36 patients (34%) a repeated USGFNA was done, and 26 patients (25%) died or were lost to follow up. Malignancy was found in 35% of operated patients (15/43); 37% of biopsies following category 3 (10/27), and 31% of category 4 (5/16). Mean TSH levels (mg %) were higher in the malignant vs. benign group (2.63 Vs 2.03) but with no statistically significant difference (P=0.44).

When excluding all patients who were lost to follow up or deceased, benign disease, diagnosed by either in histology or repeated cytology,

was found in 75% of the nodules that were primarily defined as BSRTC category 3(41/55, 28 by histology, 13 by cytology). Similarly, 79% of BSRTC category 4 were found to have benign disease (19/24, 17 by histology, 2 by cytology).

The clinical follow-up outcome of the patients is summarized in (Table 1).

After multivariate statistical analysis, no statistically significant difference was found between the sonographic characteristics of benign and malignant nodules, and correlation for malignancy was not found. The different characteristics are presented in (Table 2).

The presence of 2 or more of the 5 sonographic features known to be associated with malignancy which were included in this study (hypoechogenicty, presence of microcalcifications, irregular borders, intranodular vascularity and solidity of the nodule) were analyzed. No statistical difference was found between the malignant and the benign group (50% vs. 38% respectively, p=0.374). Since solid texture was found in 86% of malignant nodules and in 75% of benign nodules, a further analysis was done, after excluding the solid texture feature which may have acted as a confounder. The presence of 2 or more of the 4 remaining features (hypoechogenicty, presence of microcalcifications, irregular borders and intranodular vascularity), revealed a statistically significant difference between malignant and benign group (43% vs. 23% respectively, p=0.035).

Additional sonographic features including spongiform lesion, depth larger than width and nodules with comet tail sign were found scarcely in this group and therefore were not included in the statistical analysis.

	BSRTC Category 3 (n) 72% (76)	BSRTC Category 4 (n) 28% (29)	Total (n) (105)
Operated	36% (27)	56% (16)	41% (43)
Repeat FNA without change	20% (15)	20% (6)	20% (21)
RFNA benign	17% (13)	7% (2)	14% (15)
Lost to follow up \ deceased	27% (21)	17% (5)	25% (26)

BSRTC - Bethesda System for Reporting Thyroid Cytopathology

Table 1: Clinical follow up outcome of all patients with BSRTC category 3 and 4.

	Benign (n=28)	Malignant (n=15)	p-value
Age (range)	30 (15.2-34.9)	20.6 (11.9-29.2)	0.796
Male	11	5	0.813
TSH (mg%)	2.05	2.63	0.44
Physical examination characteristics			
Multinodular goiter	7	6	0.047
Hard nodule	10	5	0.985
Ultrasonographic features			
Nodule size average (range) mm	31.7 (16-48.8)	20.7 (11.9-29.3)	0.118
Solid texture	21	12	0.725
Pure Hypoechoic Nodule	7	7	0.321
Irregular borders	3	4	0.173
Microcalcifications	3	4	0.240
Intranodular vascularity	9	5	0.503

Table 2: Patient, physical examination and ultrasound characteristics of thyroid nodules of benign and malignant groups.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Solid texture	86	25	36	80	46
Pure Hypoechoic Nodule	46	75	50	72	65
Irregular borders	27	89	60	69	67
Microcalcifications	27	89	60	69	67
Intranodular vascularity	33	68	36	63	56

Table 3: Accuracy of known thyroid nodule ultrasound features associated with malignancy.

Sonographic features which formerly were correlated with malignancy, such as hypoechogenicty, presence of microcalcifications, irregular borders, intranodular vascularity and solidity of the nodule were analyzed for sensitivity, specificity, NPV, PPV and accuracy. Microcalcifications and irregular borders had specificity of 89%. Solid texture had 86% sensitivity, with 80% NPV. Sensitivity was lacking in all other features. None of the features, apart from solid texture, exceeded 75% in PPV, NPV and accuracy. Results are summarized in (Table 3).

Discussion

The purpose of this study was to evaluate the benefits of SUS in the assessment of indeterminate thyroid nodule - BSRTC category 3 and 4. It is the second research addressing surgeon performed ultrasound in the evaluation of the indeterminate thyroid nodule and the first report of SUS relating to the Bethesda classification system. As reported by Mendez et al. [8], a routinely use of ultrasound as a complementary part of the physical examination may alter clinical decision regarding proper management and follow up of the patient, and may favor conservative follow up over surgery.

SUS has been performed in our institution since 2008, evaluating thousands of patients. All US were performed by a single senior surgeon (M.Y.), thus eliminating possible variability in the results due to the "user dependence" nature of US. All FNA's were interpreted by a dedicated pathologist (J.D.), thus eliminating potential bias.

Different publications have described different sonographic features which correlated with malignancy [8,10,14,16-24]. These included hypoechogenicty, irregular border, solid texture, presence of microcalcifications, intranodular vascularity and height larger than width. The ability of a single sonographic feature to predict malignancy is a matter of controversy. While some groups found poor predictive value for a single sonographic parameter [16], other publications, including SUS related publications, have found a statistically significant difference between the sonographic features of the benign and malignant nodule [8,14,17-25]. In our research, no statistically significant difference was found in any sonographic feature between the malignant and benign nodules. Most publications agree that a combination of features increases the likelihood of malignancy, as well as improving specificity and PPV [8,14,16,19-21,24]. Our study showed that solid texture is a very sensitive, yet not specific feature, and therefore might confound other sonographic features. After excluding solid texture, a combination of 2 or more known sonographic features associated with malignancy was significantly higher in the malignant group (43% vs. 23%, p=0.035). A PPV of 60% was calculated, correlating with Mendez et al. [8]. Therefore, we suggest that the presence of 2 or more sonographic features other than solid texture in an indeterminate nodule is highly suggestive for malignancy and should promote surgery for further evaluation and treatment.

The majority of the known sonographic features associated with malignancy were lacking clinically importance as reflected by

sensitivity, predictive values and accuracy, with the exception of 90% specificity measured for microcalcifications and irregular borders and 87% sensitivity for solid texture. These results are consistent with previous reports [8,16,18].

The reported rate of malignancy for BSRTC category 3 is 5-25% (depending on patient selection), and 15-30% for BSRTC category 4 [1-3,18]. In our study, 37% of the nodules with AUS cytology were found malignant in biopsy, a significantly higher rate than reported. The rate of nodules with SFN was 31%, corresponding with the higher rates of previous reports. We believe this higher prevalence of malignancy is the effect of a careful patient selection for thyroid surgery. When including repeated benign FNA results, the percentage of BSRTC category 3 and BSRTC category 4 nodules found to be benign matched previous results. We believe that this data represent the importance of clinical judgment in the management of patients with indeterminate cytology: assessing which patients are more likely to have malignancy and should be referred to surgery, and which patients can be managed conservatively with repeated FNA and US follow-up. Though no single parameter was found to have significant correlation to malignancy, we suggest that the routine use of US by the attending surgeon contributed to the higher percentage of malignancy found in our group of patients with BSRTC category 3. Our experience has shown that while surgeon performed US may improve preoperative assessment and patient selection for surgery, US features should be regarded with caution and should always be assessed in relations to other clinical considerations, such as known risk factors, patient's adherence to follow up etc.

The major limitation of this study is its small sample size of operated patients (n=43). The small size is partly due to the heterogeneous nature of patients with indeterminate nodule, reflecting the fact that the majority of these nodules are benign, and surgery should be carefully selected. In addition, 25% of the patients were lost to follow up in our institution, some of them after being recommended for surgery. It is reasonable to assume that a substantial part of these patients had surgery in other institutions. Though expected to be the majority of the patients, the large group of unoperated patients may influence the study's results, since it is not possible to determine unequivocally the benign nature of a nodule without a histological proof.

The decision to focus on a narrow subgroup of patients during a relatively short time frame resulted in a small sample size of patients. Indeed, to better appreciate the value of SUS in the assessment of the thyroid nodule, future studies should be based on a larger group of patients for a longer follow-up period, analyzing detailed and standardized SUS findings relative to all Bethesda cytological categories and compared to the gold standard which is histopathology for all cases.

Our study has shown that though a single US feature has very limited value in preoperative predication of malignancy in the indeterminate nodule, a combination of 2 features, other than solid texture, is suggestive for malignancy, and such patients should be recommended for surgery.

The dilemma of managing indeterminate nodules is not solved yet. SUS did not seem to provide clear indications for surgery, based on sonographic features alone. Yet, our high yield of malignancy in the BSRTC category 3 nodules may be explained by an overall better clinical decision making, which may be the result of the use of SUS.

Genetic testing had recently shown promising results for predicting malignancy in indeterminate nodules, with a NPV of 95% [2], and may replace current workup for this group of patients. Until genetic testing are commonly used and considered standard of care, we recommend head and neck surgeons to use US as part of their routine follow-up, together with history and physical examination.

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