Radiologic and Clinical Predictors Of Malignancy in the Follicular Lesion of Undetermined Significance of the Thyroid

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ABSTRACT

Background: The Bethesda 2007 Thyroid Cytology Classification defines follicular lesion of undetermined significance (FLUS) as a heterogeneous category of cases that are not convincingly benign nor sufficiently atypical for a diagnosis of malignancy. Various ultrasonographic characteristics of a thyroid nodule have been associated with a higher likelihood of malignancy, and certain clinical features may also increase the likelihood of malignancy in patients. This study is designed to determine the ultrasonographic and clinical predictors of malignancy in the FLUS category.

Design: A search through the cytology files at our institution from January 2008 to December 2010 was made for cases with diagnosis of FLUS. Cases with follow-up surgical intervention formed the cohort of this study. Surgical pathology and ultrasonographic findings were reviewed. Clinical information was obtained from medical records. The clinical and radiologic findings were correlated with the final surgical pathology diagnosis.

Results: A total of 140 cases of FLUS with corresponding surgical intervention were identified (112 females and 28 males). There was 75% malignancy rate in nodules with irregular contours, compared with 50% in nodules with regular outlines. Nodules demonstrating calcifications showed 57% malignancy rate, compared with 50% in nodules without calcifications. Malignancy rate in solid nodules was 50%. For cases with a final ultrasound diagnosis of indeterminate to suspicious, 61% were positive on surgical resection. The rates of malignancy in patients with radiation exposure, symptomatic nodules and positive family history of thyroid cancer were 22%, 57% and 33%, respectively. BRAF mutation was demonstrated in 57% of malignant cases and none of benign cases.

Conclusion: No single clinical or ultrasonographic feature or combination of features is adequately sensitive or specific to identify all malignant nodules. However, a combination of solid nodules, nodules with irregular contours, symptomatic nodules and positive BRAF mutation have high predictive value for malignancy in patients with a cytologic diagnosis of FLUS.

BACKGROUND

Thyroid nodules are a common clinical entity; based upon recent data, approximately 4-7% of the US population has palpable thyroid nodules, and as much as 60% of the population has nonpalpable nodules. Despite the high number of thyroid nodules in these patients, the occurrence of malignancy in all patients with thyroid nodules remains relatively low, ranging between 5% and 7%. Contemporary preoperative management of thyroid nodules relies upon the use of ultrasonographic evaluation, percutaneous fine needle aspiration (FNA) and cytologic interpretation, whether in isolation or in tandem. While FNA cytology is an effective means of evaluating thyroid nodules, in up to 10-30% of cases, cytology is indeterminate and cannot be easily classified as benign, suspicious, or overtly malignant. Despite the widespread use and clinical efficacy of FNA, cytologically indeterminate thyroid nodules continue to present a major diagnostic issue for clinicians.

The Bethesda 2007 Thyroid Cytology Classification was developed to refine cytology definitions and improve communication and clinical management. The creation of a new category, atypia/follicular lesion of undetermined significance (AUS/FLUS), was designated for use when the cytologic and/or architectural atypia encountered is of an insufficient degree to qualify for any of the suspicious or malignant categories. The Bethesda classification recommends that the AUS/FLUS category should constitute <7% of all FNA results. This study was designed to determine the ultrasonographic and clinical predictors of malignancy in the FLUS category.

DESIGN

This study retrospectively evaluated 140 patients with a preoperative FNA diagnosis of FLUS and corresponding surgical intervention between January 2008 and December 2010. Preoperative ultrasound evaluation of nodules was undertaken in 138 of 140 cases. The ultrasonographic evaluation included documentation of nodule size, laterality, focality, contour, consistency and the presence or absence of calcifications. Preoperative FNAs were performed with multiple passes of a 22-gauge needle on site. All initial diagnoses of FLUS were reviewed at the daily Intradepartmental Cytopathology Consensus Conferences. The final reports of histologic diagnoses were retrieved from our files. Entry criteria for this study required at least one cytologic diagnosis of FLUS according to Bethesda 2007 Thyroid Cytology Classification. Patient data and clinical information were obtained from medical records. Where applicable, Chi-square analysis and Fisher's exact tests were performed to evaluate quantitative variables for statistical significance, with a value of $p<0.05$ indicating statistical significance.

RESULTS

Table 1: Clinical Features in Thyroid Nodules

Clinical Features	BENIGN	MALIGNANT	*P value*
Gender	53 F, 18 M (2.9:1)	58 F, 10 M (5.8:1)	
Family History			
Positive (n=9)	6 (67%)	3 (33%)	*0.176*
Negative (n=66)	28 (42%)	38 (58%)	
Radiation Exposure			
Yes (n=9)	7 (78%)	2 (22%)	*0.069*
No (n=54)	21 (39%)	33 (61%)	
Symptomatic Nodules			
Yes (n=46)	19 (41%)	27 (59%)	*0.999*
No (n=25)	11 (44%)	14 (56%)	

Table 2: Radiologic Features in Thyroid Nodules

Radiologic Features	BENIGN	MALIGNANT	*P value*
Average Size (cm)	2.32	1.90	
Shape			
Spherical (n=76)	37 (49%)	39 (51%)	***0.039***
Irregular (n=19)	4 (21%)	15 (79%)	
Calcifications			
Yes (n=35)	15 (43%)	20 (57%)	*0.542*
No (n=74)	37 (50%)	37 (50%)	
Consistency			
Solid (n=110)	55 (50%)	55 (50%)	*1.000*
Cystic (n=5)	2 (40%)	3 (60%)	
Mixed (n=18)	9 (50%)	9 (50%)	

Table 3: Pathologic Diagnosis versus Ultrasound Diagnosis

Ultrasound Diagnosis	BENIGN	MALIGNANT
Probable Benign (n=15)	9 (60%)	6 (40%)
Indeterminate (n=77)	29 (38%)	48 (62%)
Suspicious (n=3)	2 (67%)	1 (33%)
Unlisted (n=2)	1 (50%)	1 (50%)

Table 4: BRAF mutation analysis

Final Diagnosis	BRAF negative	BRAF positive	Total	*P value*
BENIGN	19	0	19	***0.0003***
MALIGNANT	10	13	23	
TOTAL	29	13	42	

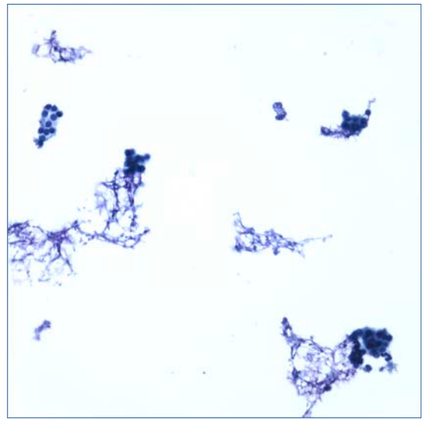

Figure 1: Predominant microfollicular architecture absence of colloid

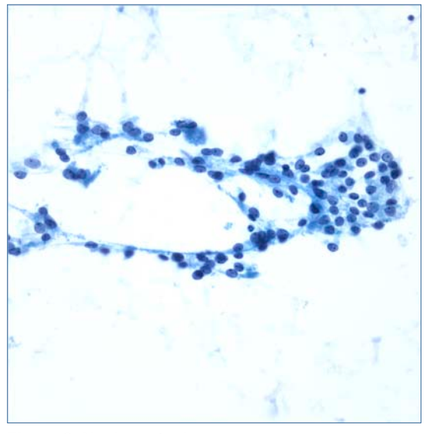

Figure 2: Nuclear atypia

A total of 140 cases of FLUS with corresponding surgical intervention were identified (112 females and 28 males). Cases were stratified into benign and malignant categories based on final histopathologic diagnosis.

Regarding clinical features in the selected cases, there was no significant statistical difference between benign and malignant nodules with reference to family history ($p=0.176$), radiation exposure ($p=0.069$) and presence of symptoms ($p=0.999$).

Regarding radiologic features in the selected cases, there was a 79% malignancy rate in nodules with irregular contours compared to a 51% malignancy rate in those with regular contours, which is a statistically significant finding ($p=0.039$). Nodules with calcifications on US demonstrated a 57% malignancy rate, whereas those without calcifications demonstrated a malignancy rate of 51% ($p=0.542$). Data regarding nodular consistency demonstrated a 50% malignancy rate in solid nodules (55/110), and the consistency comparison between benign and malignant nodules was found to be nearly identical ($p=1.000$).

Preoperative ultrasonographic diagnosis was stratified by the performing radiologist into probable benign, indeterminate and suspicious categories. For cases in the probable benign category, 40% (6/15) of cases were found to be malignant following resection. For cases in the indeterminate category, 62% (48/77) were found to be malignant following resection. For cases in the suspicious category, 33% (1/3) were found to be malignant following resection. In total, in cases with a final ultrasound diagnosis of indeterminate to suspicious, 61% were positive (i.e., malignant) on surgical resection.

Finally, BRAF mutation analysis was performed in 42 out of 140 total cases. The BRAF V600E mutation was demonstrated in 57% (13/23) of malignant cases and none of benign cases ($p=0.0003$).

CONCLUSIONS

- No single clinical or ultrasonographic feature or combination of features is adequately sensitive or specific to identify all malignant nodules. However, a combination of features such as symptomatic nodules, nodules with irregular contours, enhanced clinico-radiologic suspicion for malignancy and positive BRAF mutation have high predictive value for malignancy in patients with cytologic diagnosis of FLUS.
- The Bethesda Thyroid Cytology Classification was developed to refine cytology definitions and improve communication and clinical management. Ongoing experience with the current classification system, combined with efforts to understand the efficacy of various clinical and radiologic criteria, will undoubtedly lead to improvements in the detection of malignancy in the follicular lesion of undetermined significance of the thyroid.

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