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Management of thyroid nodules initially classified as benign: ultrasonographic features as a criterion for repetition of fine-needle aspiration

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ABSTRACT

Aims: Nodular thyroid disease is highly prevalent in the adult population. The primary objective in the management of thyroid nodules is to distinguish malignant lesions from benign ones. Following ultrasound (US)-guided fine-needle aspiration (FNA), malignancy is detected in only 3% to 12% of cases. However, in clinical practice, false-negative rates ranging from 1.3% to 11.5% in nodules classified as benign can introduce uncertainty into the management process. Early identification of distinct ultrasonographic features associated with malignancy may not only reduce unnecessary repeat FNA procedures but also help prevent diagnostic delays caused by false-negative results.

Methods: A retrospective review was performed of 513 nodules that underwent repeat FNA biopsies within 6 to 12 months over a 5-year period. US features (number and size of nodules, growth in nodule size, echotexture, echogenicity, presence of microcalcifications, cervical lymphadenopathy, and lymphadenopathy progression) were compared with cytology results to determine which sonographic findings warrant repeat biopsy and which support clinical follow-up.

Results: Repeat FNA was performed on 513 thyroid nodules initially classified as benign, with malignancy detected in 15 cases (2.9%). US features significantly associated with increased malignancy risk included microcalcifications, hypoechoic solitary nodules, enlarging hypoechoic solitary nodules, accompanying lymphadenopathy, and progressive lymphadenopathy. In contrast, nodule number, size, growth, and echotexture alone were not significant predictors of malignancy. US characteristics such as cystic composition, isoechogenicity, and hyperechogenicity were more commonly observed in benign nodules.

Conclusion: This study recommends repeat FNA for hypoechoic solitary nodules, enlarging hypoechoic solitary nodules, nodules with microcalcifications, and those associated with lymphadenopathy. In contrast, repeat FNA is not advised for cystic nodules or solid nodules without hypoechogenicity.

Keywords: Cone-beam computed tomography, mandible, mental foramen, premolar, radiology

INTRODUCTION

Nodular thyroid disease is very common among adults. The use of ultrasound (US) as a routine part of thyroid exams has led to detection rates as high as 68%.[1,2] The main purpose in the management of thyroid nodules is to differentiate malignancy. US-guided fine-needle aspiration (FNA) is the gold standard diagnostic tool to determine the management of the thyroid nodule.[3] After FNA, most nodules are diagnosed as benign, and only about 3–12% are found to be malignant.[4] Guidelines recommend clinical follow-up when a nodule is initially diagnosed as benign.[1,5] However, false-negative results ranging from 1.3% to 11.5% can make it difficult to manage benign nodules in clinical practice.[6,7] This study aims to clarify the necessity of FNA by identifying which US features are associated with an increased risk of malignancy in thyroid nodules initially diagnosed as benign. To this end, the US characteristics of the nodules and the results of repeated FNA were evaluated. This way, malignant nodules missed due to false-negative results can be detected with repeat FNA, and unnecessary repeat FNAs can be reduced.

METHODS

Ethics

All procedures complied with the Declaration of Helsinki and local ethical standards. This study has been approved by the Researches Ethics Committee of Başkent University Faculty of Medicine and Health Sciences (Date: 28.01.2015, Decision No: KAl 5/16).

Patients and Data Acquisition

A retrospective review was performed on patients who initially received a benign diagnosis and underwent repeat FNA between January 2009 and February 2014. Patients included in the study were those who underwent FNA of the same thyroid nodule, with detailed US reports available prior to both the initial and subsequent procedures. During the study period, a total of 531 nodules underwent repeat FNA. After excluding 18 nodules with inadequate cytology (n=11) or suspicious pathology (n=7) that did not undergo surgery or further FNA, 513 nodules were included in the final analysis. Exclusion criteria were: (i) nodules lacking adequate US documentation before FNA, (ii) patients with multinodular goiters where nodule correspondence between procedures was uncertain, (iii) patients who had repeat FNA from different nodules, and (iv) nodules with inadequate or suspicious cytology not followed by surgery or repeat aspiration.

Patient demographics, including gender, age and the interval between FNAs, were obtained from hospital records. US examinations were performed using high-resolution US machines by several radiologists with a minimum of 5 years of experience in thyroid imaging. Nodule characteristics were extracted from radiology reports and included: (i) size (<1 cm or ≥1 cm), (ii) internal structure (solid, cystic, or mixed), (iii) echogenicity (hypoechoic, isoechoic, hyperechoic, or mixed), (iv) number of nodules (solitary or multinodular), (v) presence of microcalcifications, (vi) associated cervical lymphadenopathy, defined as short-axis diameter >1 cm, and (vii) growth in lymph nodes, defined as ≥20% increase in at least two dimensions.[8]

Repeat FNA cytology results were classified into four categories: benign, suspicious, malignant, and inadequate specimens.[9] Nondiagnostic aspirates were excluded from final analysis unless repeated and adequate. The interval between the initial and repeat FNA, as well as any changes in sonographic features or cytology category, were recorded for all included cases.

Technique

All FNAs were performed under US guidance using a 21-gauge needle, with 2–3 passes per nodule. In cystic nodules with a solid component, the solid portion was targeted for aspiration. The aspirates were processed using conventional smear techniques and stained with Papanicolaou and May-Grünwald-Giemsa stains.

Statistical Analysis

For the evaluation of data, descriptive statistics were used. Numerical variables were expressed as mean±standard deviation, median, minimum, and maximum values, while categorical variables were presented as frequencies and percentages. The rates of malignancy associated with US findings were analyzed using cross-tabulations and presented as counts and percentages. To assess the diagnostic performance of US features in predicting malignancy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. For statistically significant findings, Fisher's exact test and the Fisher-Freeman-Halton test were used. Variables that were significant in univariate analyses were included in a multivariate logistic regression using the Backward LR elimination method to determine the best model for predicting malignancy. Results of the logistic regression analysis were reported with odds ratios (ORs), p-values, and 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS 21.0 for Windows software package.

RESULTS

Of the 513 nodules initially diagnosed as benign, 15 (2.9%) were identified as malignant, while 498 (97.1%) remained benign. The mean interval between FNA procedures was 237 days (range: 181 to 341 days). The study group included 387 female and 126 male patients aged between 17 to 87 years (median, 62±15.4 years). Six nodules in male and 9 nodules in female group were malignant. Statistical analysis revealed that gender had no significant effect on malignancy (p=0.218).

The characteristics of the nodules in the study population and their US findings are summarized in **Table 1**.

Nodule size distribution showed 34.3% of nodules were ≤1 cm and 65.7% were >1 cm, with similar malignancy rates of 3.4% and 2.7%, respectively. There was no significant difference in malignancy when infracentimetric nodules were compared with supracentimetric nodules (p=0.783).

Solid nodules had higher rate of malignancy (3.5%) than mixed nodules (1.4%) however it was not significant (p=0.361). Cystic echo-structure was a significant feature for benign cytology (p<.001).

Among echogenicity types, hypoechoic nodules represented 48.9% of the total and showed the highest malignancy rate at 5.2% (p=0.021). Isoechoic and hyperechoic nodules were all benign (p<0.001), whereas nodules with mixed echogenicity had a malignancy rate of 2.1%.

Regarding nodule number, solitary nodules showed a higher malignancy rate (7.2%) than multiple nodules (1.9%) (p=0.014). Hypoechoic solitary nodules had a significantly higher rate of malignancy than hypoechoic nodules in multinodular thyroid gland or non-hypoechoic solitary nodules (p<0.005). Nodule growth was observed in 18.7% of the nodules, with a malignancy rate of 8.3%, which was higher compared to nodules without growth (1.7%). Among hypoechoic nodules, those with growth demonstrated an even higher malignancy rate of 23.3%, compared to 1.7% in hypoechoic nodules without growth. These findings suggest that nodule growth, particularly in hypoechoic nodules, is strongly associated with an increased risk of malignancy (p<0.005).

Table 1. Characteristics of thyroid nodules by benign and malignant status

Nodule feature	Benign, n (%)	Malignant, n (%)	Total, n (%)
All nodules	498 (97.1%)	15 (2.9%)	513 (100%)
Gender			
Male	120 (95.2%)	6 (4.8%)	126 (24.6%)
Female	378 (97.7%)	9 (2.3%)	387 (75.4%)
Nodule number			
Solitary	90 (92.8%)	7 (7.2%)	97 (18.9%)
Multiple	408 (98.1%)	8 (1.9%)	416 (81.1%)
Echo-structure			
Solid	385 (96.5%)	14 (3.5%)	399 (77.8%)
Cystic	43 (100%)	0 (0%)	43 (8.4%)
Mixed	70 (98.6%)	1 (1.4%)	71 (13.8%)
Echogenicity			
Hypoechoic	238 (94.8%)	13 (5.2%)	251 (48.9%)
Isoechoic	76 (100%)	0 (0%)	76 (17.5%)
Hyperechoic	90 (100%)	0 (0%)	90 (14.8%)
Mixed echogenicity	94 (97.9%)	2 (2.1%)	96 (18.7%)
Nodule size			
≤1 cm	170 (96.6%)	6 (3.4%)	176 (34.3%)
>1 cm	328 (97.3%)	9 (2.7%)	337 (65.7%)
Nodule growth			
Present	88 (91.7%)	8 (8.3%)	96 (18.7%)
Absent	410 (98.3%)	7 (1.7%)	417 (81.3%)
Microcalcification			
Present	127 (93.4%)	9 (6.6%)	136 (28.5%)
Absent	371 (98.4%)	6 (1.6%)	377 (73.5%)
Lymphadenopathy			
Present	25 (83.3%)	5 (16.7%)	30 (5.8%)
Absent	473 (97.9%)	10 (2.1%)	483 (94.2%)
Lymph node growth			
Present	17 (85%)	3 (15%)	20 (3.9%)
Absent	481 (97.6%)	12 (2.4%)	493 (96.1%)
Subgroups of hypoechoic nodules			
Solitary hypoechoic	45 (86.5%)	7 (13.5%)	52 (10.1%)
Multiple hypoechoic	453 (98.3%)	8 (1.7%)	461 (89.9%)
Solitary hypoechoic with growth	23 (76.7%)	7 (23.3%)	30 (5.8%)
Solitary hypoechoic without growth	475 (98.3%)	8 (1.7%)	483 (94.2%)

Notes: Percentage distribution of ultrasound findings and gender in benign and malignant groups

The presence of microcalcifications was detected in 28.5% of nodules and correlated with an increased malignancy rate of 6.6%, compared to 1.6% in nodules without microcalcifications (p<0.005). Cervical lymphadenopathy was identified in 5.8% of cases, with a malignancy rate of 16.7%, while lymph node growth was noted in 3.9% of nodules and associated with malignancy in 15% of these cases (p<0.005).

Sensitivity, specificity, PPV, NPV, p values and OR of the significant US findings are given in **Table 2**.

DISCUSSION

FNA is the most effective preoperative diagnostic method for determining thyroid malignancy.[1,4] Malignant or suspicious nodules and follicular neoplasm are proposed to surgery while benign nodules are followed-up.[10] However, benign cytology does not rule out the possibility of malignancy and FNA repetition has been advised for the detection of false negative cases.[7,11,12] Repetition was found to increase the accuracy, sensitivity and specificity of the FNA and reduce the false negative results from 6.7% to 0.8%. Our study revealed that 2.9 % of the nodules had a false negative initial FNA result and a final diagnosis of malignancy was made with FNA repetition after 6 months. This result was compatible with previous reports.[7,13]

Previous studies have demonstrated that repeat FNA can be effective in detecting occult malignancies.[7,11] However, it has also been reported that in nodules initially diagnosed as benign, repeat cytology yields benign results in over 90% of cases, suggesting limited additional diagnostic value.[4,11-14] Considering the low malignancy rates, repeat FNA should not be entirely disregarded in follow-up protocols. Nevertheless, to avoid subjecting a large patient population to unnecessary procedures, repeat FNA indications should be applied more selectively.

The most practical way to restrict the indications for repetition seems to be classifying the nodules according to the US features. In the population subject to FNA repetition, US features can be used to identify nodules with a higher probability of malignancy.[1,2] Thus, diagnosis of masked malignancy can be achieved without exposing a large proportion of patients to repeat FNAs.

Primary FNA indications based on ultrasonographic features have been clearly defined in the literature.[1,2] US

Table 2. Logistic regression analysis of significant ultrasound findings and risk of malignancy

Ultrasound finding	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p value	Odds ratio
Hypoechoic nodule	86.7	35.8	5.2	99.5	0.021	3.2
Solitary nodule	46.7	81.9	7.2	98.1	0.014	3.96
Hypoechoic solitary nodule	46.7	91	13.5	98.3	0.001	5.01
Nodule growth present	53.3	82.3	8.3	98.3	0.003	5.31
Growing hypoechoic solitary nodule	46.7	95.4	23.3	98.3	<0.001	13.3
Microcalcification	60	74.5	6.6	98.4	0.005	4.86
Lymphadenopathy	33.3	95	16.7	97.9	0.001	10.96
Lymph node growth	20	96.6	15	97.5	0.017	–

Notes: Statistically significant results (p<0.05), Abbreviations: PPV: Positive predictive value, NPV: Negative predictive value

plays a key role in identifying nodules with an increased risk of malignancy. Solid hypoechoic structure, absence of a hypoechoic halo, irregular margins, a taller-than-wide shape, microcalcifications, marked intranodular vascularity, and accompanying cervical lymphadenopathy are among the main features associated with a higher likelihood of malignancy.[2,15] However, the significance of these US findings in distinguishing between benign and malignant nodules has been reported to vary across different studies.[16]

This study found that solid echo-structure was not significantly associated with malignancy, whereas cystic echo-structure was strongly correlated with benign cytology (p<0.001). Similarly, hypoechogenicity alone was a significant US feature for malignancy, while isoechogenicity and hyperechogenicity were significantly associated with benign cytology (p<0.001). Although some previous studies have reported hypoechogenicity as a significant predictor of malignancy, others have not.[12,13] Therefore, cystic nodules and non-hypoechoic solid nodules without additional suspicious US features may not require repeat FNA during follow-up.

Hypoechoic solitary nodules and growing hypoechoic solitary nodules both demonstrated a significantly increased risk of malignancy. Hypoechoic solitary nodules increased the specificity for malignancy to 91%. Although they comprised only 10.1% of all nodules in the study population, they accounted for 46.7% of malignant nodules and only 9% of benign nodules. When accompanied by growth, specificity further increased to 95.4%. These findings suggest that hypoechoic solitary nodules, and especially those that are growing, should be closely monitored with repeat FNA biopsy to avoid missing malignancies.

Consistent with previous studies, our findings demonstrated that the presence of microcalcifications is highly specific and significantly associated with an increased risk of malignancy.[1,2,12,13] Moreover, our results indicate that repeat FNA should be considered mandatory during the follow-up of initially benign nodules exhibiting microcalcifications to ensure early detection of malignant transformation.

Our study also showed that there was no significant difference among infracentimetric and supracentimetric nodules regarding malignancy in FNA repetition. US features of echogenicity, structure and microcalcification were superior criteria for FNA repetition compared to nodule size. This aligns with previous research showing no significant difference in size between benign and malignant nodules.[17,18] In contrast to nodule size, growth was significantly more common in malignant (53.3%) than benign nodules (17.7%) and was found to be highly specific for malignancy if present in hypoechoic solitary nodules. Like previous studies, our study showed that nodule growth without other specific US features was not a significant factor in increased malignancy risk.[5,12,13]

In our study, the presence of lymphadenopathy demonstrated high specificity (95%) and a significant association with malignancy (p=0.001), indicating its strong predictive value. Lymph node growth also showed high specificity (96.6%) and a significant correlation with malignancy (p=0.017), although its sensitivity was lower. These findings support the role of lymphadenopathy as an important US feature in evaluating malignancy risk in thyroid nodules. Similar results have been reported in the literature, emphasizing that lymph node enlargement and structural changes are closely linked to malignancy.[19,20] Therefore, patients with detected lymphadenopathy or lymph node growth should be closely monitored and considered for repeat FNA when necessary.

Limitations

US evaluations were performed by different radiologists, which may have introduced interobserver variability in imaging findings. Furthermore, certain sonographic features strongly associated with malignancy—such as margin irregularity, taller-than-wide shape, and intranodular vascularity—were not assessed due to inconsistent availability in retrospective records. Malignancy diagnoses were based solely on FNA cytology, and histopathological confirmation through surgical specimens was not available for all cases. Lastly, the low number of malignant cases (n=15; 2.9%) limited the statistical power, necessitating cautious interpretation of the results.

CONCLUSION

This study suggests that FNA repetition to all nodules with initially benign cytology is not justified. FNA repetition should not be performed in cystic, isoechoic and hyperechoic nodules. Solitary hypoechoic nodules, nodules with microcalcification and accompanying cervical lymphadenopathy have increased risk of malignancy and should always undergo FNA repetition within 12 months despite initially benign cytological diagnosis.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study has been approved by the Researches Ethics Committee of Başkent University Faculty of Medicine and Health Sciences (Date: 28.01.2015, Decision No: KAI 5/16).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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