Usefulness of Ultrasonography in Conjunction with Fine-Needle Aspiration Biopsy for Determining Malignancy in Thyroid Nodules

Tiroid Nodüllerinde Maligniteyi Saptamada İnce İğne Aspirasyon Biyopsisi ile Birlikte Ultrasonografinin Yararlılığı

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ABSTRACT

Objective: To determine the value of ultrasonography (US) in conjunction with fine-needle aspiration biopsy (FNAB) for predicting malignancy in thyroid nodules.
Material and Methods: We reviewed 219 patients who underwent surgery for nodular goiter. All patients had undergone preoperative FNAB, whose results were reported using the Bethesda criteria. We compared clinical and US findings between patients with benign and malignant tumors. We determined the diagnostic accuracy of FNAB for detecting malignancy in thyroid nodules. In addition, we determined the usefulness of US findings for detecting thyroid cancer in patients with inconclusive FNAB results.
Results: According to the final histopathological evaluation, 167 (76.3%) patients had benign tumors, 52 (23.7%) patients had malign tumors. FNAB had 83.4% accuracy, 84.9% sensitivity, 82.8% specificity, 66.1% positive predictive value and 93.2% negative predictive value. Age, nodule size, number of nodules, nodule composition (solid/cystic), hyperechogenicity and macrocalcification/no calcification did not differ between benign and malignant tumors. However, microcalcification, hypoechogenicity, irregular margins and increased intranodular flow were significantly more common in malignant tumors. Hypoechogenicity, microcalcification and increased intranodular flow increased the malignancy risk by 13.63, 6.391 and 6.659 times, respectively.
Conclusion: FNAB is the most effective way of detection of the malignancy in thyroid nodules. Hypoechogenicity, irregular margins, microcalcifications and increased intranodular flow on US were related with increased malignancy risk, and may help predict the necessity of absolute surgical decision in patients with inconclusive FNAB results.

Keywords
Thyroid; thyroid nodule; ultrasonography; fine-needle aspiration biopsy

ÖZET

Amaç: Tiroid nodüllerinde ince iğne aspirasyon biyopsisi (İİAB) ile birlikte ultrasonografinin (USG) maligniteyi öngörmedeki önemini belirlemektir.
Gereç ve Yöntemler: Nodüler guatr nedeniyle cerrahi geçiren 219 hastayı değerlendirmeye aldık. Tüm hastalara operasyon öncesinde İİAB yapıldı ve bu hastaların sonuçları Bethesda kriteleri kullanılarak rapor edildi. Benign ve malign tümörlü hastalar arasında klinik ve USG bulgularını karşılaştırdık. Tiroid nodüllerindeki maligniteyi saptamada İİAB'nin tanı değerini belirledik. Buna ek olarak, İİAB'nin sonuçsuz kaldığı hastalarda tiroid kanserini saptamak için USG bulgularının yararlılığını belirledik.
Bulgular: Nihayi patoloji sonuçlarına göre 167 (%76.3) hastanın benign, 52 (%23.7) hastanın malign tümörü vardı. İİAB'nin %83.4 kesinliği, %84.9 duyarlılığı, %82.8 özgüllüğü, %66.1 pozitif prediktif değeri ve% 93.2 negatif prediktif değeri vardı. Yaş, nodül boyutu, nodül sayısı, nodülün kompozisyonu (solit/kistik), hiperekojenite ve makrokalsifikasyon/kalsifikasyon olmaması, benign ve malign tümörlerde farksızdı. Fakat, mikrokalsifikasyon, hipoekojenite, düzensiz marjin ve artmış intranodüler akım, anlamlı bir biçimde malign tümörlerde daha yaygındı. Hipoekojenite, mikrokalsifikasyon ve artmış intranodüler akım malignite riskini sırasıyla 13.63, 6.391 and 6.659 kez arttırıyordu.
Sonuç: İİAB Tiroid nodüllerindeki maligniteyi tespit etmenin en etkili yoludur. USG'de hipoekojenite, düzensiz marjin, mikrokalsifikasyon ve artmış intranodüler akım artmış malignite riskiyle ilşkilidir ve bu bulgular, İİAB'nin sonuçsuz kaldığı hastalarda mutlak cerrahi kararını öngörmede bize yardımcı olabilir.

Anahtar Sözcükler
Tiroid; tiroid nodül; ultrasonografi; ince iğne aspirasyon biyopsisi

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INTRODUCTION

Thyroid nodules are a common clinical problem. They are detected in up to 67% of the general population on high-resolution ultrasonography (US), and the incidence rate of malignancy in thyroid nodules is 5-10%.[1,2] Thyroid nodules are classified as adenomas, carcinomas or hyperplastic lesions on the basis of their macroscopic and microscopic histological features.[3] These nodules warrant removal when they are large enough to be symptomatic, or if there is a risk of malignancy. US-guided fine-needle aspiration biopsy (FNAB) is reported to be the most accurate predictor of malignancy in a nodule.[4] However, FNAB may have limited diagnostic value owing to high rates of insufficient samples and false-negative results.[5] In the case of tumors that are found or suspected to be malignant on FNAB examination, there is no doubt about the need for surgery. However, when FNAB indicates a benign tumor or if the biopsy sample is insufficient, further tests or findings that can clarify whether the tumor is malignant or benign are required.

Certain US features have been identified as predictors of malignancy, such as hypoechogenicity, microcalcifications, and irregular and blurred margins.[6,7] Additionally, large nodules (≥2 cm), nodules that enlarge during follow-up and solitary nodules are considered to pose a malignancy risk, though there is some debate over the matter.[8,9]

In this study, we aimed to determine the diagnostic value of FNAB and US findings, and the contribution of US in deciding whether surgery is indicated in patients with benign results on FNAB or insufficient FNAB samples.

MATERIAL AND METHODS

Patient selection

The present study was conducted on subjects who had undergone total thyroidectomy, lobectomy or lobeisthmectomy due to nodular goiter at Haseki Research and Training Hospital between 2007 September and 2013 December. The decision to operate was primarily based on FNAB results (malignant, suspicious for malignancy, follicular neoplasm or atypia of unknown significance). In subjects with benign results or insufficient samples, the decision to operate was made if there were suspicious US (Philips Hd 15) findings (nodule >2 cm, presence of microcalcification, hypoechogenicity, increased intranodular flow or irregular margins), cervical lymphadenopathy, compressive symptoms or a significant increase in size during follow-up (6-12 months). We retrospectively reviewed patients who had undergone primary thyroidectomy, and included 219 patients with detailed preoperative US and FNAB evaluations in this study. Patients with abnormal thyroid-function tests were excluded from the study and referred to the endocrinology department.

The study protocol was approved by our institutional ethics committee, and all patients' written informed consent forms were obtained from their medical records.

US findings

Subjects who had detailed US findings (size, echogenicity, margins, calcifications and vascularity) were reviewed in this study. Nodule size was defined as the largest diameter of the nodule. Nodule echogenicity (hypoechogenic, isoechogenic or hyperechogenic) was based on the echogenicity of the surrounding thyroid tissue. Margins were classified as regular or irregular (blurred, peripheral halo). Calcifications were classified as microcalcifications (<3 mm, hyperechoic foci with or without acoustic shadow), macrocalcifications (>3 mm, with acoustic shadow) or no calcifications. Vascularization of the nodule was evaluated using color Doppler and power Doppler.

FNAB

Nodules larger than 10 mm or those that measured at least 7 mm and were accompanied with suspicious US findings such as irregular margins, hypoechogenicity and microcalcifications were subjected to FNAB. FNAB was performed under US guidance with two passes of a 22-gauge needle by any of radiology specialist in the Radiology Department, randomly. In the case of multinodular goiter, FNAB was conducted on the two biggest nodules and on suspicious nodules measuring at least 7 mm. The FNAB results were reported using the Bethesda criteria as follows: insufficient sample (class 1), benign (class 2), atypia of unknown significance (class 3), follicular neoplasm (class 4), suspicious for cancer (class 5) and cancer (class 6). Patients in Bethesda class 1 underwent FNAB at least two times. To determine the predictive value of FNAB, we classified the FNAB results as follows: Group 1 (Bethesda classes 2–6) and Group 2 (Bethesda classes 2 and 6; definitive results only). In group 1, Bethesda classes 3, 4 and 5 were assumed to indicate malignant nodules.

Data and statistical analyses

We compared the FNAB results to the final histopathological findings in order to determine the diagnostic value of FNAB. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of FNAB were determined using the Pearson chi-square test, Fisher exact test and Fisher–Freeman–Halton test. The Student t test and Mann–Whitney U test were used to compare parametric variables and the Pearson chi-square test, Fisher exact test and Fisher–Freeman–Halton test used to compare non-parametric variables between patients with benign and malignant nodules, as determined according to the final histopathological results. Descriptive statistics were expressed as mean ± standard deviation or percentages. In order to determine the risk of malignancy according to the US findings, multivariate logistic regression analysis was performed. Additionally, we compared independent variables such as age and US findings to determine the actual contribution of these variables in the decision to operate in patients with class-1 or class-2 FNAB results.

All analyses were performed using Number Cruncher Statistical System 2007 and Power Analysis and Sample Size 2008 statistical software (Utah, USA). P-values less than 0.05 were considered statistically significant.

RESULTS

General characteristics

The mean age of the patients was 44.51±13.35 years (range, 15-77 years). There were 41 (18.7%) male patients, and 178 (81.3%) female patients. The mean nodule size was 30.74±14.95 mm (range, 6-100 mm). Of the 219 patients, 37% had solitary nodules, and 63% had multiple nodules.

US

There were no significant differences between patients with benign tumors and those with malignant tumors in terms of age, size of nodules, number of nodules, composition (solid or cystic) of nodules, and macrocalcification or non-calcification of nodules. However, microcalcification, hypoechogenicity, irregular margins and increased intranodular flow were significantly more common in malignant tumors than in benign tumors (Table 1).

Table 1. Comparison of age and US findings according to final histology results.

(n=219)		Benign (n=167) Mean±SD	Malignant (n= 52) Mean±SD	p
Age		43.72±13.57	47.02±12.41	[a]0.120
Nodule size (mm)		31.31±14.57 (29.00)	28.90±16.11 (25.50)	[b]0.154
		n (%)	n (%)	
Number of nodules	Solitary	58 (71.6)	23 (28.4)	[c]0.215
	Multiple	109 (79.0)	29 (21.0)	
Echogenicity(n=169)	Hypoechoic	50 (63.3)	29 (36.7)	[d]0.001**
	Hyperechoic	26 (86.7)	4 (13.3)	
	İzoechoic	55 (91.7)	5 (8.3)	
Composition	Solid	94 (75.8)	30 (24.2)	[c]0.497
	Cystic	36 (72.0)	14 (28.0)	
	Cystic degenerate	37 (82.2)	8 (17.8)	
Calcifications	Absent	112 (86.8)	17 (13.2)	[d]0.001**
	Microcalcification	37 (51.4)	35 (48.6)	
	Macrocalcification	18 (100.0)	0 (0.0)	
Margins	Regular	115 (78.8)	31 (21.2)	[d]0.001**
	Hypoechoic halo	45 (81.8)	10 (18.2)	
	Eggshell calcification	6 (100.0)	0 (0.0)	
	Irregular	1 (8.3)	11 (91.7)	
Increased intranodular flow	Absent	147 (82.6)	31 (17.4)	[c]0.001**
	Present	20 (48.8)	21 (51.2)	

[a]Student t test; [b]Mann-Whitney U test; [c]Pearson chi-square test; [d]Fisher-Freeman-Halton test.
*p<0.05; **p<0.01.

Among patients with class-1 and class-2 nodules, age, size of nodules, number of nodules, composition (solid or cystic) of nodules, echogenicity of nodules, and macrocalcification or non-calcification of nodules did not significantly differ between those with benign tumors and those with malignant tumors. However, microcalcification, irregular margins and increased intranodular flow significantly more common in malignant tumors than in benign tumors (Table 2).

The presence of hypoechogenicity, microcalcification and increased intranodular flow increased the risk of malignancy by 13.63 (95% confidence interval [CI]: 3.82-48.61), 6.391 (95% CI: 2.5-16.27) and 6.659 (95% CI: 2.19-20.22) times, respectively. The highest effect was seen in the case of hypoechogenicity (Table 3). The specificities and sensitivities of the various suspicious US findings are shown in Table 4.

FNAB

The FNAB results were as follows: insufficient sample, 35 (16%) patients; benign, 119 (54.3%) patients; atypia of unknown significance, 8 (3.7%) patients; follicular neoplasm, 12 (5.5%) patients; suspicious for cancer, 31 (14.2%) patients; and cancer, 14 (6.4%) patients (Table 5). According to the final histopathological evaluation, 167 (76.3%) patients had benign tumors, 45 (20.6%) had papillary cancer (including two with microcarcinoma), 2 (0.92%) had medullary cancer, 2 had lymphoma and 3 (1.4%) had follicular cancer (Table 5). The general distribution of other variables is also shown in Table 5. The comparison between the FNAB results and final histopathological findings is presented in Table 6.

Of the 35 class-1 nodules, 1 (2.8%) each was a papillary cancer and a lymphoma. Of the 119 class-2 nodules, 8 (6.7%) were papillary cancers. Of the 8 class-3 nodules, 5 (62.5%) were papillary cancers. Of the 9 class-4 nodules, 2 (22.2%) were papillary cancers and 3 (33.3%) were follicular cancers. Of the 34 class-5 nodules, 22 (64.7%) were papillary cancers and 1 (2.9%) was a lymphoma. Of the 14 class-6 nodules, 12 (85.7%) were papillary cancers and 2 (14.2%) were medullary cancers.

There was a significant relationship between the FNAB results and the final histological results ($p<0.01$). The sensitivity, specificity, PPV, NPV and accuracy rate of FNAB for detecting cancer were 84.9%, 82.8%,

Table 2. Comparison of the ultrasonographic findings of benign and malignant tumors in patients with Bethesda class 1 & 2 nodules.

Bethesda classes 1 & 2 (n=154)		Benign (n=144) Mean±SD	Malignant (n=10) Mean±SD	p
Age (years)		44.01±13.53	45.50±11.37	[a]0.735
Nodule size (mm)		31.85±14.83 (30.00)	27.20±13.87 (24.00)	[a]0.206
		n (%)	n (%)	
Number of nodules	Solitary nodule	48 (90.6)	5 (9.4)	[b]0.314
	Multiple nodules	96 (95.0)	5 (5.0)	
Echogenicity (n = 122)	Hypoechoic	41 (89.1)	5 (10.9)	[c]0.207
	Hyperechoic	25 (92.6)	2 (7.4)	
	Isoechoic	48 (98.0)	1 (2.0)	
Composition	Solid	80 (93.0)	6 (7.0)	[c]1.000
	Cystic	30 (93.8)	2 (6.2)	
	Cystic degenerate	34 (94.4)	2 (5.6)	
Calcifications	Absent	94 (96.9)	3 (3.1)	[c]0.012*
	Microcalcification	34 (82.9)	7 (17.1)	
	Macrocalcification	16 (100.0)	0 (0.0)	
Margins	Regular	100 (94.3)	6 (5.7)	[c]0.002**
	Hypoechoic halo	37 (97.4)	1 (2.6)	
	Eggshell calcification	6 (100.0)	0 (0.0)	
	Irregular	1 (25.0)	3 (75.0)	
Increased intranodular flow	Absent	129 (96.3)	5 (3.7)	[c]0.004**
	Present	15 (75.0)	5 (25.0)	

[a]Mann-Whitney U test; [b]Fisher exact test; [c]Fisher-Freeman-Halton test.
*p<0.05; **p<0.01.

Table 3. Logistic regression analysis and odds ratios of three suspicious US findings.

	p	Odds ratio	95% CI Lower	95% CI Upper
Hypoechogenicity	0.000**	13.629	3.821	48.609
Microcalcification	0.000**	6.391	2.510	16.275
Increased intranodular flow	0.001**	6.659	2.192	20.228

US: Ultrasonography; CI: Confidence interval.

Table 4. Sensitivities and specificities of US characteristics for the detection of thyroid cancer.

	Sensitivity (%)	Specificity (%)
Irregular margins	33.2	83.3
Increased intranodular flow	40.38	88.02
Hypoechogenicity	76.32	61.83
Microcalcification	67.31	75.17

66.1%, 93.2% and 83.4%, respectively, in Group 1 (Bethesda classes 2-6), and 63.6%, 100%, 100%, 93.2% and 93.9%, respectively, in Group 2 (Bethesda classes 2 and 6).

DISCUSSION

US-guided FNAB is generally considered the most reliable means of predicting malignancy within a thyroid nodule, owing to its sensitivity (65-98%) and specificity (72-100%).[2,4] This test has greatly helped to reduce the number of thyroidectomies.[2,4] The results of the present study were consistent with the literature. The sensitivity and specificity of FNAB were 84.9% and 82.8%, respectively, in group 1 (Bethesda classes 2-6), and 63.6% and 100%, respectively, in group 2 (Bethesda classes 2 and 6). The difference between the groups was attributable to the suspicious FNAB results (Bethesda classes 3-5) in group 1. A definitive diagnosis of malignancy (class 6) on FNAB is generally consistent with the final histology results. However, if the FNAB results are indeterminate, the final histological report may be "malignant" or "benign". Therefore, the specificity of FNAB was lower in group 1 than in group 2. In both groups, the sensitivity and specificity were compatible with previous reports in which only definitive results were evaluated.[2,4,5]

In the evaluation of thyroid nodules for malignancy, nodule size is especially important. Several studies have suggested that the risk of malignancy increases with nodule size.[8,10-13] However, other studies have reported contrasting findings. [5,14-16] Kamran et al. analyzed the records of 4955 patients, and used a size threshold of 2 cm for predicting malignancy.[8] Alexander et al. reported that benign nodules may decrease in size, but more often, they increase in size, albeit slowly.[12] Banks et al. reported an interesting claim that nodules measuring 2.5 cm had the lowest likelihood of malignancy.[14] For smaller nodules, the risk increased by 53% for every 1-cm decrease in size. For larger nodules, the risk increased by 39% for every 1-cm increase.[14] According to the literature, the malignancy rate in thyroid nodules that are 4 cm or larger and exhibit indeterminate cytology varies from 10% to 30%.[13,17-19] According to Bommelis et al., nodules that are symptomatic or measure about 4 cm warrant surgical excision; in this situation, a FNAB is recommended, as it may preoperatively determine whether a total thyroidectomy is to be performed or a lobectomy.[20] However, nodule size was a significant criterion in the decision to operate if the FNAB results were "benign" or "insufficient".[5] In brief, estimations of malignancy risk and surgical decisions based on nodule size alone are controversial. In the present study, although size was a significant factor when deciding to operate, we did not observe any difference in nodule size between malignant and benign tumors. We operated on nodules that measured 2 cm or more, even if the FNAB result was "benign" or "insufficient sample" and there were no suspicious findings. In addition, we operated on patients with "malignant" or "suspicious" FNAB results, regardless of nodule size. Most of these patients had small (<2 cm) nodules. In patients without other relevant findings, nodule size may be useful to determine the necessity of surgery. However, we must emphasize that our results regarding nodule size are not reliable in all situations. Surgeons must be aware that nodule size is not the only factor that should be taken into account when making the decision to operate. A meta-analysis or prospective clinical studies with diverse subjects may end the debate on this subject.

The other suspicious US characteristics were superior to nodule size for identifying nodules that are likely to be malignant. These characteristics include the presence of microcalcifications, hypoechogenicity and increased intranodular flow.[21,22] In the study by Rosa´rioal., 23.5% of nodules with indeterminate cytology were malignant, and the authors found suspicious characteristics on US in 76% of these nodules.[13] In a recent analysis, Kihara et al. observed that malignancy was directly associated with suspicious US findings.[16] These findings were similar to those of Maia et al., who assessed the correla-

Table 5. General distribution of variables.

		(Min-Max)	(Median±SD)
Age (years)		15-77	44.51±13.35
Nodule size (mm)		6-100	30.74±14.95
		(n)	(%)
Sex	Female	178	81.3
	Male	41	18.7
Number of nodules	Solitary	81	37.0
	Multiple	138	63.0
IIAB-Bethesda classification	Insufficient	35	16.0
	Benign	119	54.3
	Atypia of unknown significance	8	3.7
	Follicular neoplasm	12	5.5
	Suspicious for cancer	31	14.2
	Malignant	14	6.4
Final histology	Benign	167	76.3
	Papillary cancer	45	20.6
	Medullary cancer	2	0.9
	Lymphoma	2	0.9
	Follicular cancer	3	1.4
Echogenicity (n = 169)	Hypoechoic	79	46.7
	Hyperechoic	30	17.8
	Isoechoic	60	35.5
Composition	Solid	124	56.6
	Cystic	50	22.8
	Cystic degenerative	45	20.5
Calcification	Absent	129	58.9
	Microcalcification	72	32.9
	Macrocalcification	18	8.2
Margins	Regular	146	66.7
	Hypoechoic halo	55	25.1
	Eggshell calcification	6	2.7
	Irregular	12	5.5
Increased intranodular flow	Absent	178	81.3
	Present	41	18.7

Table 6. Comparison of fine-needle aspiration biopsy and final histology results.

	Final Histology					
IIAB-Bethesda classification; (n)	**Benign**	**Papillary cancer**	**Medullary cancer**	**Lymphoma**	**Follicular cancer**	**p**
Insufficient material	33	1	0	1	0	[a]0.001**
Benign	111	8	0	0	0	
Atypia of unknown significance	5	3	0	0	0	
Follicular neoplasm	7	2	0	0	3	
Suspicious for cancer	11	22	0	1	0	
Malignant	0	12	2	0	0	

[a]Fisher-Freeman-Halton test; ** p<0.01.

tions of the cytological variables of the Bethesda classification with clinical, US and scintigraphic data from patients with thyroid nodules with indeterminate cytology.[13] Malignancy was found in 68.4% of nodules with suspicious US characteristics and 14.8% of those with normal US findings.[13] According to Kwak et al., if the initial cytologic results indicate benign thyroid nodules, the likelihood of the nodule actually being benign is 98.1%.[23] When a thyroid nodule has benign results at both the initial and repeat FNAB, the likelihood increases to 100%.

The likelihood of having a benign thyroid nodule with suspicious US features was lower (79.6%) than having a benign thyroid nodule with negative US features (99.4%).[23] Li et al. reviewed the US features of 115 nodules in 104 patients and found that microcalcifications, central flow and irregular borders were directly associated with malignant thyroid nodules.[19] According to Leenhardt et al., hypoechogenicity on US has a moderate PPV (50-63%) for malignancy in thyroid nodules, with high sensitivity (75%) and specificity (61-83%).[18] Gonzalez-Gonzalez et al. studied the US characteristics of 341 thyroid nodules and found that microcalcifications were the only variable that was significantly associated with malignancy.[24] Iannuccilli et al. reported intrinsic calcification as the only statistically significant predictor of malignancy (35.3% sensitivity and 94.4% specificity).[15] Furthermore, the presence of a "snowstorm" pattern of calcification was 100% specific for malignancy. Echogenicity, echo structure, shape, border classification and grade of internal vascularity did not significantly differ between benign and malignant nodules in the above study. The authors recommended FNAB in all nodules with microcalcifications.[15] Moon et al. analyzed 1083 thyroid nodules and found that increased intranodular flow is the most common distinction between benign and malignant nodules.[25] In the present study, the most important predictor of malignancy was hypoechogenicity, followed by increased intranodular flow and microcalcification. Fish et al. investigated suspicious US features, and reported that microcalcification, hypoechogenicity and increased intranodular flow had sensitivities of 52%, 81% and 67%, respectively, and specificities of 83%, 53% and 81%, respectively.[26] In the present study, the corresponding sensitivity values were 40%, 76% and 76%, and the corresponding specificity values were 88%, 61% and 88%. We also analyzed these US characteristics in patients with Bethesda class-1 & 2 nodules. In these subjects, the decision to operate was based on suspicious clinical and US findings. We found that malignancy was significantly related to irregular margins, increased intranodular flow and microcalcification in these patients. Astonishingly, hypoechogenicity was not significantly related with malignancy in these patients. Logistic regression analysis of the data of all the study patients showed that the highest effect was seen in the case of hypoechogenicity. Therefore, the result about hypoechogenicity among class-1 and class-2 patients is puzzling. The retrospective nature of the present study may be accountable for this finding.

CONCLUSION

FNAB is the most effective way of detection of the malignancy in thyroid nodules. In patients with thyroid nodules, US findings, in conjunction with FNAB results, can also be used as a predictor of malignancy. Specifically, hypoechogenicity, irregular margins, microcalcification and increased intranodular flow are related with an increased risk of malignancy. These findings could help surgeons to determine the necessity of surgery, particularly, when the FNAB result is "benign", or the FNAB sample is insufficient. However, age, nodule size, nodule composition (cystic vs. solid), number of nodules and macrocalcifications or no calcifications were not related with increased malignancy risk.

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