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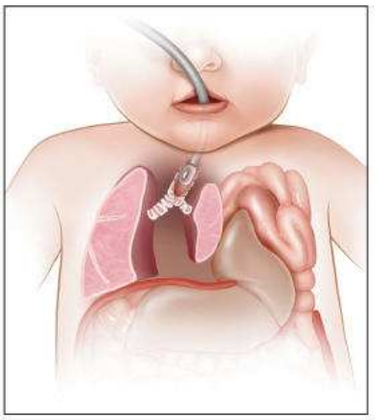

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Sonographic Features of Thyroid Follicular Carcinoma in Comparison With Thyroid Follicular Adenoma

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Article includes CME test

Objectives—The purpose of this study was to determine the sonographic features of thyroid follicular carcinoma in comparison with thyroid follicular adenoma.

Methods—This retrospective study included 36 pathologically proven follicular carcinomas (5 widely invasive and 31 minimally invasive) and 52 follicular adenomas in 88 patients who underwent thyroid surgery. We analyzed the sonographic features of each tumor, including maximum diameter, peripheral halo, echogenicity, echo texture, calcifications, and nodularity. The frequencies of the sonographic features were compared by χ^2 and Fisher exact tests between follicular adenomas and carcinomas. The relative risk of malignancy was evaluated by logistic regression analysis.

Results—Predominantly solid contents, hypoechoic echogenicity, a heterogeneous echo texture, the presence of calcifications, and an absent or irregular thick halo were associated with follicular carcinoma ($P < .05$). Logistic regression analysis demonstrated that predominantly solid contents, a heterogeneous echo texture, and the presence of calcifications were associated with significant increases in the relative risk of follicular carcinoma (odds ratios, 9.4, 24.9, and 25.6, respectively; $P < .01$).

Conclusions—Sonography could provide useful information for differentiating follicular carcinoma from follicular adenoma.

Key Words—follicular adenoma; follicular carcinoma; general ultrasound; sonography; thyroid

Thyroid nodules are common; 10% to 67% of adults have thyroid nodules, and nearly 50% of the population have thyroid nodules at autopsy.[1] As determined by fine-needle aspiration cytologic evaluation, approximately 20% of nodules are diagnosed as follicular neoplasms.[2] Follicular neoplasms of the thyroid include benign follicular adenoma and follicular carcinoma.[3] However, the malignant potential of a follicular neoplasm can rarely be determined by cytologic evaluation alone, and most patients are advised to undergo surgery for evaluation of capsular or vascular invasion, which is a prerequisite for the diagnosis of follicular carcinoma, whereas histologic evaluation reveals that about 80% are benign lesions.[4]

Sonography has dramatically increased the number of incidentally detected thyroid nodules, and the prevalence of thyroid nodules has been reported to range from 35% to 46% with the use of a high-frequency transducer, with a 4.4% incidence of malignancy among nonpalpable thyroid nodules.[5] A sonographic examination of the thyroid gland is recommended in all patients with a thyroid nodule to help characterize the nodule as well as to examine the rest of the thyroid gland for other nodules.[6,7]

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Abbreviations

NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value

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Several retrospective studies have described the sonographic appearance of thyroid follicular neoplasms and suggested that a hypoechoic mass on sonography, as well as male sex, a nodule size larger than 40 mm, and a solitary mass, indicates an increased risk of thyroid follicular carcinoma.[8–10] However, Hagag et al[11] reported that sonographic findings did not have a predictive role for carcinoma in follicular tumors. The purpose of this study was to determine the sonographic features of follicular neoplasms and to determine whether sonography can be used to differentiate follicular adenoma from follicular carcinoma.

Materials and Methods

Patients

This study was approved by our Institutional Review Board. Because the patients' data were evaluated retrospectively and anonymously, no written informed consent was necessary. We retrospectively selected 51 patients who received a diagnosis of follicular carcinoma and 118 patients who received a diagnosis of follicular adenoma by thorough histopathologic analysis of resected hemithyroidectomy or total thyroidectomy specimens from a pathology report database between January 1, 2010, and August 1, 2012. A total 15 patients with a diagnosis of follicular carcinoma and 66 patients with a diagnosis of follicular adenoma were excluded from the study because they lacked presurgical sonography.

A total of 36 patients (27 female and 9 male; median age, 50.6 years; range, 21–87 years) were included as cases of follicular carcinoma in the study. They included 31 cases with minimally invasive carcinoma (25 female and 6 male; median age, 49.2 years; range, 21–87 years) and 5 cases with widely invasive carcinoma (2 female and 3 male; median age, 59.8 years; range, 39–75 years). A total of 52 control patients (40 female and 12 male; median age, 51.4 years; range, 23–79 years) with a diagnosis of follicular adenoma were selected during the study period from a total of 579 cases of follicular adenoma that resulted in surgical removal by selecting every 50th case arranged by medical record number.

Sonography

Sonographic examinations of the thyroid gland were performed with a Hi Vision 900 system (Hitachi Medical Corporation, Inc, Tokyo, Japan), an Acuson Sequoia 512 system (Siemens Medical Solutions, Mountain View, CA), or an iU22 system (Philips Healthcare, Bothell, WA) equipped with a commercially available 8–15-MHz linear transducer. Two sonologists (with >5 years of experience in thyroid sonography) conducted a retrospective consensus review of the sonograms without knowledge of clinical information or final diagnoses. The images were presented for readers on a picture archiving and communication system in an anonymous random fashion.

Nine variables were recorded, including the patient's age, sex, and maximum tumor diameter, and the following sonographic features were assessed for each nodule: halo sign (thin, unevenly thick, or incomplete), cystic changes (predominantly solid [<25%], mixed [25%–75%], or predominantly cystic [>75%]), internal echogenicity (anechoic, hyperechoic, isoechoic, hypoechoic, or markedly hypoechoic), echo texture (homogeneous or heterogeneous), the presence of calcifications (absent, microcalcifications, macrocalcifications, or peripheral calcifications), and nodularity (multiple or solitary).

Histopathologic Examination of Surgical Specimens

Surgical samples were sectioned before fixation for macroscopic examination. Whole thyroid glands were examined grossly using multiple 5-mm slices to accurately diagnose mutifocal lesions. Specimens were fixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin-eosin for histologic examinations. Follicular carcinomas and adenomas were diagnosed on the basis of their degrees of tumor capsular or vascular invasiveness. A follicular neoplasm with tumor invasion into but not through the entire capsule was considered a follicular adenoma. Vascular invasion was defined as tumor penetration into a large-caliber vessel within or outside the capsule. Follicular carcinomas are generally subdivided into minimally invasive and widely invasive variants based on morphologic criteria. Minimally invasive follicular carcinoma is an encapsulated tumor with microscopic penetration of the tumor capsule without vascular invasion. Widely invasive follicular carcinoma is characterized by the presence of extensive invasion of the capsule vessels, extension beyond the tumor capsule into the adjacent thyroid parenchyma or extrathyroidal tissue, or both.[12]

Statistical Analysis

Statistical analysis was performed with commercially available software (SPSS version 17.0; SPSS Inc, Chicago, IL). An unpaired Student *t* test was used to compare continuous variables (maximum diameter and age). χ^2 and Fisher exact tests were used to compare categorical variables. $P < .05$ was considered statistically significant. The relative risks of malignancy were evaluated by multivariate logistic regression analysis. The significantly different variables between follicular adenomas and carcinomas in the χ^2 or Fisher

exact test were selected as binary predictor variables in the models to check for possible confounding effects. For logistic regression, results were considered significant when calculated odds ratios (ORs) were greater than 1.0 and when the lower score for the 95% confidence limit was also greater than 1.0.

We also investigated the usefulness of sonography and clinical features that had statistically significant differences between follicular carcinomas and adenomas by evaluation of the sensitivity, specificity, overall accuracy, positive predictive value (PPV), and negative predictive value (NPV) for each parameter.

Results

Patient Demographic Data

A total of 36 patients had follicular carcinoma, and 52 had follicular adenoma. There was no significant difference in mean age or sex between patients with follicular carcinoma (mean age ± SD, 50.6 ± 16.1 years; male to female ratio, 9:27) and those with follicular adenoma (mean age, 51.4 ± 13.7 years; male to female ratio, 12:40; $P > .05$).

Sonographic Features of Follicular Adenomas and Carcinomas

The sonographic features of follicular adenomas and carcinomas are shown in Table 1. The mean size of follicular carcinomas was slightly larger than that of follicular adenomas, but there was no significant difference between their mean maximum diameters (32.3 ± 15.8 versus 28.9 ± 11.6 mm; $P > .05$).

In terms of echogenicity, most follicular carcinomas were hypoechoic (69.4%), whereas most follicular adenomas were isoechoic (63.5%; $P < .05$; Figures 1–3). Markedly hypoechoic nodules were rare in both follicular carcinomas and adenomas (2.8% and 1.9%, respectively). Most follicular carcinomas had a heterogeneous echo texture (83.3%), commonly appearing as hypoechoic or multinodular, whereas a homogeneous echo texture was more commonly seen in follicular adenomas (80.8%; $P < .05$). Concerning internal contents, a predominantly solid pattern was more common for follicular carcinomas (100.0%), whereas follicular adenomas more commonly had a mixed or predominantly cystic pattern (61.5%; $P < .05$). The presence of calcifications was more common in follicular carcinomas compared with adenomas (55.6% versus 7.7%; $P < .05$). Peripheral calcifications were observed in 27.8% of follicular carcinomas and 1.9% of follicular adenomas ($P < .05$; Figure 4), and internal microcalcifications or macrocalcifications were observed in 27.8% of follicular carcinomas and 5.8% of follicular adenomas ($P < .05$). Among the follicular carcinomas, all of the widely invasive carcinomas had calcifications (80% with internal calcifications and 20% with peripheral calcifications). An incomplete or unevenly thick halo was more commonly seen in follicular carcinomas (69.4%), whereas a thin halo was more common in follicular adenomas (86.5%; $P < .05$). The ratio of solitary nodules in follicular carcinomas was slightly higher than that in adenomas, but no statistically significant difference was noted (33.3% versus 21.2%; $P > .05$).

For follicular tumors with a predominantly solid pattern, the sonographic features of follicular adenomas and carcinomas are shown in Table 2. It was shown that an incomplete or unevenly thick halo, hypoechoic echogenicity, a heterogeneous echo texture, and the presence of calcifications were more commonly seen in follicular carcinomas ($P < .05$).

Table 1. Clinical and Sonographic Features of Follicular Carcinoma and Adenoma

Feature	Carcinoma (n = 36)	Adenoma (n = 52)	*P* < .05
Age, y	50.6 ± 16.1	51.4 ± 13.7	
≤45	12 (33.3)	15 (28.8)	No
>45	24 (66.7)	37 (71.2)	
Sex			
Female	27 (75.0)	40 (76.9)	No
Male	9 (25.0)	12 (23.1)	
Maximum diameter, mm	32.3 ± 15.8	28.9 ± 11.6	No
≤40	28 (77.8)	43 (82.7)	
>40	8 (22.2)	9 (17.3)	
Cystic contents			Yes
Predominantly cystic (>75%)	0 (0.0)	22 (42.3)	
Mixed (25%–75%)	0 (0.0)	10 (19.2)	
Predominantly solid (<25%)	36 (100.0)	20 (38.5)	
Peripheral halo sign			Yes
Present and thin	11 (30.6)	45 (86.5)	
Incomplete/unevenly thick	25 (69.4)	7 (13.5)	
Echogenicity			Yes
Anechoic	0 (0.0)	10 (19.2)	
Hyperechoic	0 (0.0)	0 (0.0)	
Isoechoic	10 (27.8)	33 (63.5)	
Hypoechoic	25 (69.4)	8 (15.4)	
Markedly hypoechoic	1 (2.8)	1 (1.9)	
Calcifications			Yes
Absent	16 (44.5)	48 (92.3)	
Micro- or macrocalcifications	10 (27.8)	3 (5.8)	
Peripheral calcifications	10 (27.8)	1 (1.9)	
Echo texture			Yes
Predominantly homogeneous	6 (16.7)	42 (80.8)	
Heterogeneous	30 (83.3)	10 (19.2)	
Nodularity			No
Multiple	24 (66.7)	41 (78.8)	
Solitary	12 (33.3)	11 (21.2)	

Data are presented as mean ± SD and number (percent).

For all 88 follicular tumors, multivariate logistic regression analysis identified the following independent risk factors for follicular carcinoma: a predominantly solid pattern (OR, 9.403; $P < .01$), a heterogeneous echo texture (OR, 24.881; $P < .01$), and the presence of calcifications (OR, 25.555; $P < .01$). For 56 follicular tumors with a predominantly solid pattern, multivariate logistic regression analysis identified the following independent risk factors for follicular carcinoma: a heterogeneous echo texture (OR, 10.627; $P < .01$) and the presence of calcifications (OR, 15.268; $P < .01$).

Figure 1.Longitudinal sonogram of the left thyroid from a 65-year-old woman with minimally invasive follicular carcinoma. A hypoechoic solid nodule is shown.

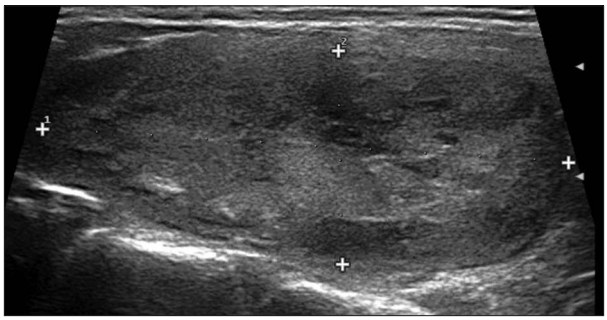


Figure 2. Transverse sonogram of the left thyroid from a 69-year-old woman with widely invasive follicular carcinoma. A hypoechoic solid nodule with a multinodular growth pattern is shown.

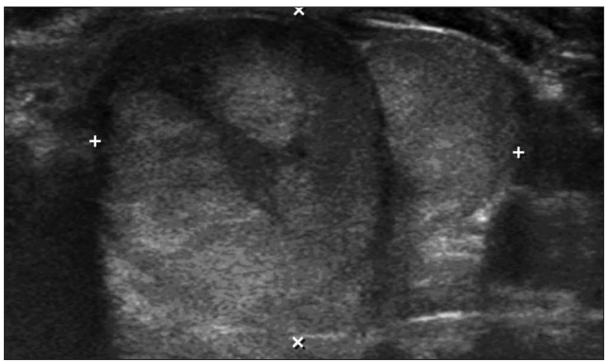
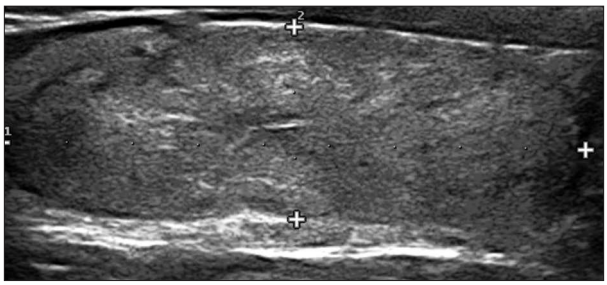


Figure 3. Longitudinal sonogram of the right thyroid from a 52-year-old man with follicular adenoma. An isoechoic solid nodule is shown.



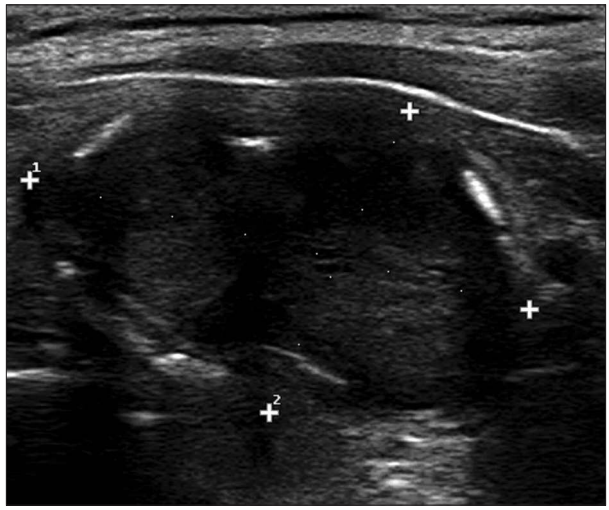
Comparison of the Sonographic Features of Minimally and Widely Invasive Follicular Carcinomas

Among 36 follicular carcinomas, 5 were widely invasive, and 31 were minimally invasive. Widely invasive carcinomas were significantly larger than minimally invasive carcinomas (46.3 ± 24.9 versus 30.3 ± 13.0 mm; $P < .05$), and calcifications were seen in all of the widely invasive carcinomas compared with only 48.4% of the minimally invasive carcinomas ($P < .05$). No significant differences were observed between widely and minimally invasive carcinomas with respect to the other sonographic features.

Diagnostic Performance of the Sonographic Features

For the differential diagnosis on sonography, the sensitivity, specificity, overall accuracy, PPV, and NPV of the sonographic and clinical findings that showed a statistically significant difference between follicular carcinomas and adenomas are listed in Table 3. It was shown that when tumors with a predominantly solid pattern were diagnosed as follicular carcinoma, the sensitivity and NPV could reach 100%, whereas the specificity (61.5%) and PPV (61.5%) were lower. Nevertheless, there was an obvious improvement in the specificity and PPV with the addition of other sonographic features that showed statistically significant differences between follicular carcinomas and adenomas. The combination of a predominantly solid pattern and the presence of calcifications achieved the highest PPV (90.9%) and specificity (96.1%). The combination of a predominantly solid pattern and a heterogeneous echo texture achieved the highest NPV (88.0%) and total accuracy (84.1%).

Figure 4. Longitudinal sonogram of the right thyroid from a 57-year-old woman with minimally invasive follicular carcinoma. A hypoechoic-isoechoic solid nodule with interrupted peripheral calcifications is shown.



Discussion

In this article, we have described the sonographic findings of follicular carcinomas in comparison with follicular adenomas. It is shown that a predominantly solid pattern, an incomplete or unevenly thick halo, hypoechoic echogenicity, a heterogeneous echo texture, and the presence of calcifications were more common in follicular carcinomas. Moreover, a predominantly solid pattern, a heterogeneous echo texture, and the presence of calcifications were found to independently predict the presence of follicular carcinomas.

Cystic degeneration has been described as a characteristic of follicular adenomas,[13] and it has been suggested that follicular carcinomas rarely become cystic.[14] In our study, it was also shown that predominantly solid contents are more common in follicular carcinomas in comparison with follicular adenomas. It can be hypothesized that the absence of internal cystic changes may be secondary to the rapid proliferation of malignant cells, which do not undergo autolysis, and degenerative cystic changes, as in a benign adenoma.[8]

Hypoechoic echogenicity has been reported as a risk factor for malignancy in thyroid nodules,[2] and hypoechoic echogenicity was more frequently seen in follicular carcinomas compared with adenomas.[8,9] This conclusion was substantiated in our study. It can be hypothesized that the presence of decreased echogenicity within a thyroid nodule may imply that the follicular cells are undergoing rapid, disordered growth with a loss of the normal orderly arrangement of follicles in normal thyroid parenchyma, which renders the tissue less echogenic than adjacent normal parenchyma.[8] In addition, tissue necrosis, hemorrhage, or both in follicular carcinomas may also be responsible for these findings.[12,15]

A halo is defined as a hypoechoic rim surrounding the neoplasm and is thought to represent a capsule surrounding a mass in resected specimens.[8] The role of the halo sign in differentiating thyroid malignancy from benignity is still controversial.[16,17] In our study, an unevenly thick halo was more common in follicular carcinomas than adenomas. These findings are in accordance with macroscopic findings that the capsule tends to be thicker and more irregular in follicular carcinomas than adenomas.[12] A possible explanation is that a progressing desmoplastic reaction or fibrosis around a slowly growing malignancy may lead to thickening of the capsule.

Calcifications, including microcalcifications, macrocalcifications, and peripheral calcifications, have been associated with an increased risk of thyroid malignancy.[18] This conclusion was substantiated in our study. However, the patterns of microcalcifications or macrocalcifications in follicular carcinomas showed a tendency to be small in number and scattered compared with the classic appearance of microcalcifications in papillary carcinoma.[9] It can be hypothesized that these calcifications may be secondary to tissue necrosis, hemorrhage, or both, which are more common in follicular carcinomas, especially in widely invasive carcinomas.[15] Peripheral calcifications originate from dystrophic calcifications and are generally considered an indicator of a benign nodule.[19,20] However, several studies have reported that peripheral calcifications could also be seen in malignant thyroid tumors, such as follicular carcinomas and papillary carcinomas, and have suggested that thyroid nodules that show interruption, thickening of peripheral calcifications, and internal hypoechogenicity should be considered suspicious lesions.[21–23]

It has long been considered that a single nodule is much more likely to be malignant than the nodules in a multinodular goiter.[24] However, various studies have

Table 2. Clinical and Sonographic Features of Follicular Tumors With a Predominantly Solid Pattern

Feature	Carcinoma (n = 36)	Adenoma (n = 20)	*P* < .05
Age, y	50.6 ± 16.1	51.8 ± 13.0	No
≤45	12 (33.3)	6 (30.0)	
>45	24 (66.7)	14 (70.0)	
Sex			No
Female	27 (75.0)	18 (90.0)	
Male	9 (25.0)	2 (10.0)	
Maximum diameter, mm	32.3 ± 15.8	28.8 ± 14.4	No
≤40	28 (77.8)	16 (80.0)	
>40	8 (22.2)	4 (20.0)	
Peripheral halo sign			Yes
Present and thin	11 (30.6)	13 (65.0)	
Incomplete/unevenly thick	25 (69.4)	7 (35.0)	
Echogenicity			Yes
Hyperechoic	0 (0.0)	0 (0.0)	
Isoechoic	10 (27.8)	13 (65.0)	
Hypoechoic	25 (69.4)	6 (30.0)	
Markedly hypoechoic	1 (2.8)	1 (5.0)	
Calcifications			Yes
Absent	16 (44.5)	18 (90.0)	
Micro- or macrocalcifications	10 (27.8)	1 (5.0)	
Peripheral calcifications	10 (27.8)	1 (5.0)	
Echo texture			Yes
Predominantly homogeneous	6 (16.7)	12 (60.0)	
Heterogeneous	30 (83.3)	8 (40.0)	
Nodularity			No
Multiple	24 (66.7)	16 (80.0)	
Solitary	12 (33.3)	4 (20.0)	

Data are presented as mean ± SD and number (percent).

Table 3. Sensitivity, Specificity, Overall Accuracy, PPV, and NPV of Sonographic Features for Differentiating Follicular Carcinoma From Follicular Adenoma

Feature	Sensitivity, %	Specificity, %	Accuracy, %	PPV, %	NPV, %
Predominantly solid	100.0	61.5	77.3	61.5	100.0
Heterogeneous echo texture	83.3	80.8	81.8	75.0	87.5
Presence of calcifications	55.6	92.3	77.2	83.3	75.0
Hypoechoic echogenicity	72.2	82.7	78.4	74.3	81.1
Absent/unevenly thick halo	69.4	86.5	79.5	78.1	80.4
Predominantly solid + heterogeneous echo texture	83.3	84.6	84.1	78.9	88.0
Predominantly solid + calcifications	55.6	96.1	79.5	90.9	75.8
Predominantly solid + hypoechoic echogenicity	72.2	86.5	80.7	78.8	81.8
Predominantly solid + absent/unevenly thick halo	69.4	86.5	79.5	78.1	80.4

reported that the frequency of thyroid cancer in patients with a solitary nodule was not different from the frequency in patients with multiple nodules.[25] It was also reported that follicular carcinomas frequently were found in multinodular thyroids.[26] This conclusion was substantiated in our study, in that most of the follicular carcinomas and adenomas were detected in cases of multinodular hyperplasia.

Nodule size has been suggested as a risk factor for follicular carcinoma, and a nodule size larger than 40 mm is associated with an increased risk of malignancy.[27] However, some studies reported that the size of a nodule is not helpful for predicting or excluding malignancy.[9,26] In our study, the mean size of follicular carcinomas was slightly larger than that of adenomas, and the percentage of nodules larger than 40 mm in follicular carcinomas was slightly higher than that in adenomas, but there was no statistically significant difference. However, widely invasive follicular carcinomas were significantly larger than minimally invasive carcinomas. These findings may indicate that larger follicular tumors with the malignant sonographic features mentioned above may indicate the possibility of widely invasive follicular carcinomas.[15]

It was reported that follicular carcinomas occur most often in patients between the ages of 45 to 49 and 60 to 70 years.[28] In our study, the age range for patients with follicular carcinomas was 21 to 87 years, and the mean age was 50.6 ± 16.1 years. There was no statistically significant difference between patients with follicular carcinoma and adenoma in terms of mean age. It has been reported that widely invasive follicular carcinoma is more common in elderly patients than minimally invasive carcinoma.[15] In our study, patients with widely invasive carcinoma tended to be older than those with minimally invasive carcinoma (59.8 ± 13.8 versus 49.2 ± 16.1 years), but there was no statistically significant difference. This finding may be explained by the small sample size of patients with widely invasive carcinoma (only 5 cases).

The finding of thyroid nodules in a male patient is known to be a more concerning finding than in a female patient.[8,29] However, in our study, there was no significant difference in sex between patients with follicular carcinoma (male to female ratio, 9:27) and those with adenoma (male to female ratio, 12:40).

Our study had some limitations. The evaluation of cases was retrospective, and there was an unavoidable selection bias. The retrospective study design prevented us from evaluating sonographic findings in real time, which might have influenced the evaluation of the interpreters. In addition, the sample size of patients with widely invasive follicular carcinoma was small, which may have prevented us from comprehensively evaluating their clinical and sonographic features. Last but not least, our study did not include color Doppler findings as a parameter for differentiation of follicular carcinomas and adenomas, although all cases in our study had color Doppler imaging performed. However, we think that retrospective interpretation of static color Doppler sonograms is not reliable. Further prospective studies will be necessary to resolve these issues.

In conclusion, a predominantly solid pattern, an incomplete or unevenly thick halo, hypoechoic echogenicity, a heterogeneous echo texture, and the presence of calcifications were significantly associated with follicular carcinoma. A predominantly solid pattern, a heterogeneous echo texture, and the presence of calcifications were independent predictors of follicular carcinoma. For the differential diagnosis on sonography, combinations of 2 or more of these sonographic features may achieve higher specificity and a higher PPV in diagnosing follicular carcinoma and may help physicians in making decisions regarding whether to proceed to thyroid surgery.

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