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High Prevalence of Carcinoma in Ultrasonography-guided Fine Needle Aspiration Cytology of Thyroid Nodules

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Abstract. Objective: The purpose of this study was to assess the rate of malignancy in thyroid nodules incidentally detected at sonography and to determine the diagnostic value of ultrasonography-guided fine needle aspiration cytology (USgFNAC) in thyroid nodules. Methods: Five hundred patients (84 men and 416 women) who had thyroid incidentalomas underwent USgFNAC at Konkuk University Hospital between August 2005 and July 2006. Thyroid sonography and guided aspiration was performed on all single nodules and on dominant nodules with suspected malignancy in cases of multinodular goiter. Results: Five hundred fifty-eight nodules from 500 patients were aspirated using ultrasonography guidance. The USgFNAC results for all patients were as follows: 307 (61.4%) benign, 108 (21.6%) suggestive of malignancy, 56 (11.2%) indeterminate, and 29 (5.8%) inadequate for cytologic diagnosis. The rate of malignancy was significantly higher in women than in men (23.6% in women vs 11.9% in men, $p<0.01$). Ultrasonographic characteristics that had a significant association with thyroid malignancy included solid echocomponent, hypoechogenecity, ill defined margin, and presence of microcalcifications ($p<0.05$). Eighty-eight patients underwent surgical resection. The positive predictive value of USgFNAC was 90.2% (74/82), and the accuracy index was 84.1% (74/88). In 80 patients with well-differentiated thyroid carcinoma after surgery, 49% (39/80) had lesions smaller than 1 cm. Conclusion: The rate of malignancy in incidental thyroid nodules on USgFNAC was 21.6%. Ultrasonographic features could be useful in differentiating between benign and malignant nodules.

Key words: Fine needle aspiration, Incidentaloma, Thyroid nodule, Thyroid carcinoma, Ultrasonography

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THYROID nodules are present in 4–7% of the general population by palpation [1–3]. The number of thyroid incidentalomas is increasing due to widely use of highly sensitive ultrasonography for routine health examinations [4]. Previous studies have reported that incidental thyroid nodules are commonly detected at a rate of 30–50% on sonography [5, 6] with a malignancy rate of about 7–15% [7–10]. Fine needle aspiration cytology (FNAC) is now established as a reliable and safe method to distinguish between benign and malignant thyroid nodules [8, 11, 12]. It has been recently reported that ultrasonography-guided fine needle aspiration cytology (USgFNAC) has improved diagnostic accuracy compared to FNAC by palpation in thyroid nodules [1, 3, 10]. However, most of these studies involved selected patient populations, and there are lacks of published studies providing a complete malignancy assessment of all thyroid nodules regardless of size. For appropriate management of thyroid nodules, it is important to assess the benignity or malignancy, and to determine the sonographic findings that may predict malignancy.

The purpose of this study was to assess the rate of malignancy in thyroid nodules incidentally detected at sonography and to determine the diagnostic value of USgFNAC in thyroid nodules. We assessed the diagnostic accuracy of USgFNAC in patients who underwent surgical resection of the thyroid gland.

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Patients and Methods

Thyroid ultrasonography was performed on 508 patients who were referred to the Division of Endocrinology and Metabolism at Konkuk University Hospital (Seoul, Korea) between August 2005 and July 2006 for the evaluation of thyroid nodules. All patients had thyroid nodules detected during thyroid sonography for routine health examination. Three-hundred nine patients (61%) were referred from Health Promotion Center in our hospital, and the other one-hundred ninety-nine patients (39%) from local clinics. Patients with suppressed TSH levels were excluded.

All patients underwent thyroid ultrasonography performed by experienced radiologists, using 10-MHz linear transducers (IU-22, Philips Medical Systems, Bothell, WA). Sonographic features of the thyroid nodules were recorded: single *vs* multiple, size, parenchymal composition (solid, mixed, or cystic), echogenicity, marginal appearance and calcifications. Size was recorded as maximum axial diameter. Parenchymal composition was classified based on assessment of the cystic portion of the nodule as follows: solid (cystic lesion less than 25%), mixed (25–74% cystic), predominantly cystic (75–99% cystic), or completely cystic. The echogenicity of each nodule relative to the thyroid parenchyma was reported as hyperechoic, isoechoic, or hypoechoic. A marginal appearance was categorized as well-defined or ill-defined. The presence or absence of calcifications was noted for each nodule, and calcifications were classified as microcalcification, septal calcification, macrocalcification, or rim calcification.

After sonographic evaluation, 500 patients (84 men and 416 women) underwent USgFNAC. Eight patients were excluded because their sonographic finding indicated completely cystic nodules smaller than 2 cm. USgFNAC was performed on all single nodules larger than 3 mm in diameter. In a multinodular goiter, USgFNAC was performed on the dominant nodule or the nodules suspected to be malignant based on sonographical features (microcalcifications, rounded shape, solid composition, nodule associated with abnormal cervical lymph nodes). Informed written consent was obtained from all subjects after explanation of the USgFNA.

USgFNAC was performed using a 21-gauge needle on a 10-ml syringe. Three to four aspirations were done per nodule. Aspirated specimens were smeared on glass slides, fixed in 95% ethanol immediately and stained using a Papanicolaou method. Cytological diagnosis was made by an experienced pathologist.

Cytologic results were recorded as follows: benign (nodular hyperplasia, lymphocytic thyroiditis), suggestive of malignancy (papillary carcinoma, poorly differentiated carcinoma, metastatic carcinoma, lymphoma), indeterminate (suspicious for follicular neoplasm, follicular cell proliferative lesions), or inadequate (fewer than six clusters of follicular thyroid cells in each preparation). Papillary carcinoma was defined as specimens showing clusters of atypical follicular cells with nuclear grooves and intranuclear pseudoinclusions.

All patients with suggestive malignant cytology or clinically suspicious of malignancy among indeteminate category were referred to surgery. Eighty-eight patients underwent surgery in our hospital, and the final diagnosis for each nodule was based on histopathological results. For postoperative staging, the American Joint Committee on Cancer (AJCC) TNM staging system was used [13].

Data were expressed as the mean ± standard deviation (SD). We analyzed results on both a per-patient and a per-nodule basis. Statistical analysis was performed using by χ^2 test. Statistical significance was accepted when the corresponding p-value was less than 0.05.

Results

Patient Characteristics

A total of 500 patients (84 men and 416 women) were included in this study. The mean age was 49.2 years, with a range of 26–75 years. Five times more women than men were included (16.8% men vs. 83.2% women).

Cytologic results of USgFNAC

After sonography, 288 of the 500 patients had solitary nodules and 212 had multiple nodules. Of the 212 patients with multiple thyroid nodules, 36 patients (2 nodules aspirated in 14 patients and 3 nodules aspirated in 22 patients) underwent FNAC in more than two nodules. Aspiration was repeated in 16 cases due to nondiagnostic report and final cytologic diagnosis was used in analysis. Nine nodules had benign cytology despite of malignant appearance in sonography, which was confirmed as benign by repeated biopsies. Five

Table 1. Cytologic results of USgFNA for patients with thyroid nodules

	Men (N = 84)	Women (N = 416)	Total (N = 500)
Benign	55 (65.5%)	252 (60.6%)	307 (61.4%)
Malignant	10 (11.9%)	98 (23.6%)*	108 (21.6%)
Papillary carcinoma	9 (90%)	95 (97%)	
Follicular carcinoma		1	
Medullary carcinoma	1		
Poorly differentiated carcinoma		1	
Metastatic adenoCa.		1	
Indeterminate	11 (13.1%)	43 (10.3%)	56 (11.2%)
Inadequate	7 (8.3%)	22 (5.3%)	29 (5.8%)

*$p<0.05$ vs men by χ^2 test.

"indeterminate" cytology turned out to be indeterminate in 3 and benign in 2. And three cases with inadequate cytology resulted in 1 benign and 2 inadequate cytology. Thus, a total of 574 USgFNAC were performed on 558 nodules from 500 patients. Of these final 558 nodules, 350 (62.7%) were benign and 116 (20.8%) were malignant, including 111 papillary carcinoma thyroid carcinoma (PTC), 2 follicular carcinoma, 1 medullary thyroid carcinoma, 1 metastatic adenocarcinoma, and 1 poorly differentiated carcinoma.

Among 36 patients having more than 2 aspirated nodules, if there were any malignant nodules, the patients were categorized as having malignant cytology and if there were any indeterminate or inadequate cytology, the patients were categorized as having 'indeterminate' or 'inadequate' cytology in per patient analysis. There were no cases having both inadequate and indeterminale nodules. Cytologic results per patient were as follows: 307 (61.4%) benign; 108 (21.6%) suggestive of malignancy (104 papillary carcinoma, 1 follicular carcinoma, 1 medullary thyroid carcinoma, 1 poorly differentiated carcinoma, 1 metastatic adenocarcinoma); 56 (11.2%) indeterminate; and 29 (5.8%) inadequate for cytological diagnosis (Table 1).

The prevalence of thyroid cancer did not differ between patients with a solitary thyroid nodule (62 of 288 patients, 21.5%) and patients with multiple nodules (46 of 212 patients, 21.7%). The rate of malignancy was higher for women than for men (23.6% in women, 11.6% in men, $p<0.01$). However, there was no significant difference in the malignancy rate according to age.

Correlation of sonographic characteristics and cytology

Sonographic characteristics of the thyroid nodules are summarized in Table 2. To determine association between sonographic features and malignancy, we compared the sonographic findings with the cytologic results. Mean diameter of all nodules was 16.4 ± 11.3 mm. Mean diameter of malignant nodules was significantly smaller than that of benign nodules (11.6 ± 8.2 mm vs. 17.8 ± 11.4 mm, $p<0.01$). Surprisingly, the malignancy rate of thyroid nodules was higher in patients with nodule less than 1 cm compared with equal to or larger than 1cm ($p<0.01$).

Those individual sonographic characteristics that showed a statistically significant difference in malignant cytology after USgFNAC were: presence of a solid component, hypoechoic nodule, ill defined margin, and presence of microcalcifications. In particular, the malignancy rate was significantly increased in solid nodules compared to nonsolid (mixed or cystic) nodules. Hypoechoic nodules had a higher rate of malignancy than isoechoic /hyperechoic nodules. An ill-defined margin was significantly associated with malignancy. The presence of microcalcification increased the likelihood of malignancy compared to the absence of calcifications, but rim calcification was favor for benign cytology.

Histopathological diagnosis after surgery

A total of 88 patients underwent surgical resection at our hospital. Final cytological and pathological diagnoses are shown in Table 3. Among 72 patients whose cytological diagnosis was papillary thyroid carcinoma, all turned out to have the same histological diagnosis except one whose diagnosis was follicular carcinoma. Patients with a cytological diagnosis of one medullary thyroid carcinoma, one metastatic adenocarcinoma or one poorly-differentiated carcinoma had the same histological diagnosis.

Fourteen of 56 patients whose cytological diagnosis was 'indeterminate' underwent thyroidectomy. Seven had papillary thyroid carcinoma, 1 had a minimally invasive follicular carcinoma, and 6 had nodular hyperplasia on histological results. The positive predictive value of USgFNAC was 90.2% (74/82), and its accuracy index was 84.1% (74/88) (Table 4).

The 80 patients with well-differentiated thyroid carcinoma after surgery were categorized according to

Table 2. Ultrasonographic Characteristics of thyroid nodules according to the result of cytology (N = 558 nodule)

characteristic	Benign	Malignant	Indeterminate	inadequate	Malignancy rate (%)	*P*-value
No. of nodule	350	116	59	33		NS
Single	167	62	40	19	62/288 (21.6)	
Multiple	183	54	19	14	54/270 (20)	
Size (mm)						<0.01
0–9.9	88	64	22	13	64/187 (34.2)	
≥10	262	52	37	20	36/371 (9.7)	
Composition						<0.01
Solid	239	112	52	21	112/424 (26.4)	
Mixed	46	2	6	4	2/58 (3.4)	
Cystic	65	2	1	8	2/76 (2.6)	
Echogenecity						<0.01
Hypoechoic	57	96	22	14	96/189 (50.8)	
Iso/Hyper	293	20	37	19	20/369 (5.4)	
Margin						<0.01
Ill-defined	17	29	11	2	29/59 (49.1)	
Well defined	333	87	48	31	87/499 (17.4)	
Calcification						<0.01
Micro	22	38	7	2	38/69 (55.1)	
Rim	13	1		3	1/17 (5.9)	
Other	5	1		1	1/7 (14.2)	
Absence	310	76	52	27	76/465(16.3)	

P-value: difference between nodules of benign and those of malignant.
NS denotes 'not significant'.

Table 3. Cytologic diagnosis by USgFNAC and histopathologic results by surgery

Cytology (n = 88)	Pathology (n = 88)
Papillary Ca (72)	Papillary Ca (71)
	Follicular carcinoma (1)
Medullary Ca (1)	Medullary Ca (1)
Poorly differenciated thyroid carcinoma (1)	Anaplastic Ca (1)
Indeterminated (14)	Papillary Ca (7)
	Follicular Carcinoma (1)
	Nodular Hyperplasia (6)

Table 4. Diagnostic accuracy of USgFNAC in histopathologically confirmed patients

Cytologic diagnosis	Surgical histopathology		
	Malignant	Benign	Total
Malignant	74	0	74
Benign	0	0	0
a Non-diagnostic	8	6	14
Total	82	6	88

Positive predictive value: 74/82 (90.2%)
Accuracy index: 74/88 (84.1%)

Table 5. Number of the patients in each TNM stages of well differenciated thyroid carcinomas

Size (mm)	I	II	III	IVA	IVB	IVC	Total
0–9.9	29		10				39
10–19.9	13		10	3	1		27
20–29.9	5		3	1			9
30–30.9	1		2	2			5
≥40				0			0
Total	48	0	26	6	1	0	80

AJCC stage (Table 5). Of the patients under 45 years old, 32 had well-differentiated thyroid carcinoma and all cases were tumor stage I. Of patients 45 years or older, 48 had well-differentiated thyroid carcinoma: 15 stage I, 26 stage III, and 7 stage IV. Remarkably, 10 of the 33 stage III or IV well-differentiated thyroid carcinomas (30%) were less than 1 cm in diameter. None of the patients had distant metastases after whole-body scan followed by high dose radioactive iodine ablation.

Discussion

The purpose of this study was to assess the malignancy rate in thyroid nodules incidentally detected at sonography and to determine the diagnostic value of ultrasonography-guided fine needle aspiration cytology (USgFNAC) in thyroid nodules.

In previous studies, which were performed without USgFNAC, thyroid cancer was detected in approximately 4–7% of patients [3, 11]. More recent studies using USgFNAC reported a 7–15% prevalence of thyroid cancer [7–10]. Previous studies used different size guidelines for USgFNAC of thyroid incidentaloma. For examples, Frates *et al.* perfomed USgFNAC selectively on patients with nodule larger than 1 cm [9]. In other studies, only thyroid nodules less than 1.5 cm were aspirated by sonographic guidance for cytologic examination [4, 8]. However, it has been routine practice at our clinic to refer all patients with incidental thyroid nodules to radiologists. Thus, our study group is large, and we further reduced selection bias by performing USgFNAC on all patients with thyroid nodules. In only one study, USgFNAC had done in all patients with thyroid nodular disease, but it did not evaluate the association between size or sonographic features of nodules and malignancy [13]. To the best of our knowledge, no other studies of USgFNAC have provided a complete clinical and sonographic assessment of all thyroid nodules regardless of size.

The malignancy rate of thyroid nodules in our study was 21.6%, which is higher than in most previous reports [8–10]. The higher rate of malignancy in our study might result from selection bias based on sonographic findings. In strict sense, definite incidental thyroid nodule was just 61% from Health Promotion Center of our hospital detected by routine health screening program. The other 39% was referred for aspiration from local clinic because of sonographically detected thyroid nodules. Therefore, it is possible that patients may be referred from local clinic when their nodules were clinically or sonographically suspicious of malignancy. However, there was no significant difference in malignancy rate of thyroid nodules between patients referred from local clinic and those referred from Health Promotion Center of our hospital. Another reason for high malignancy rate in our study might result from selective use of USgFNAC according to sonographic findings in multinodular goiter. However, previous studies have reported that there is no significant difference in the malignancy rate of patients with a single thyroid nodule and patients with multiple nodules [8, 9, 14]. In our study, the prevalence of thyroid cancer on cytology did not differ between patients with a single nodule (62/288, 21.5%) and patients with multiple nodules (46/212, 21.7%). We excluded initially only 8 patients who had completely cystic thyroid nodules. In multinodular goiter, 36 of 212 patients (17%) underwent USgFNAC for more than 2 nodules. And if a patient underwent FNAC for only dominant one nodule with benign cytology, it was considered benign. We did not have all pathological diagnoses of multiple nodules, and there may be a slight difference in malignancy rate between cytology and histology. However, of 74 patients whose cytological diagnoses were malignant, all turned out to have malignant pathology. In addition, of 14 patients who had surgery based on indeterminate cytology, 57% (8 of 14) had malignant pathology. Considering this, the true malignancy rate for thyroid incidentalomas is at least 21.6%.

The rate of inadequate sampling (lack of material, blood only) in USgFNAC was 5.8% and the rate of indeterminate findings was 11.2%. Previously, the rate of inadequate sampling for FNAC done "freehand" was 11–13% [10, 11, 15]. More recent studies using USgFNAC have reported rates of 6–7.2% [10, 12, 13]. Although the mean tumor size in our study was 16.4 ± 11.3 mm, we performed USgFNAC on all tumors larger than 3 mm. Considering that 187 of the 558 thyroid nodules (33.5%) were smaller than 1 cm, the rate of inadequate sampling for USgFNAC was low. In addition, after histopathologic examination, the positive predictive value of USgFNAC in our study was 90.2%, indicating that our procedure was more sensitive and accurate than in previous reports [10, 12].

While the use of diagnostic thyroid ultrasonography is rapidly increasing, there is debate on interpretation of thyroid US findings and on which thyroid nodule should be subjected to FNAC. Many studies have examined the relationship between sonographic features of thyroid nodules and malignancy [4, 8, 9]. Recent recommendations suggest FNAC for most nodules greater than 10–15 mm, particularly those with suspected malignancy based on sonographic features and in cases of multiple nodules, FNAC should be based on the sonographic features rather than size of each nodule. Simple cystic lesions do not require aspiration cytology [16, 17]. In our study, the sonographic characteristics that correlated with malignancy included:

solid, hypoechoic, ill-defined margin, and the presence of microcalcifications. Our findings are consistent with previous studies [4, 8, 9, 18, 19]. For rim calcification, other studies did not show a relationship to malignancy [8,9]. In our study, most nodules with rim calcification were benign (13 of 17).

Previous reports showed that there was no significant difference between nodular size and malignancy [8, 9, 20]. Interestingly, our study showed that mean diameter of malignant nodules was smaller than that of benign nodules, and that malignancy rate was significantly higher in thyroid nodules smaller than 1cm than equal to or larger than 1 cm (34.2% vs 9.7%, $p<0.01$). This result implies that smaller size per se does not guarantee lower risk of malignancy.

Among non-sonographic features, patient gender was correlated with malignancy, but age was not. Although clinical studies suggest that a nodule in men is more likely to be malignant than in women [9, 21], we didn't find these results. In our study, nodules in women were more likely to be malignant than in men. This higher incidence of malignancy may be explained by the inclusion of US examination of thyroid and breast in routine health examinations for women. It is similar to the results of another Korean report [4].

There is significant debate regarding the clinical significance of papillary microcarcinoma (PMC). The majority of PMCs are not palpable and so clinically unapparent. In the past, many PMCs were found on pathology specimens from thyroid gland removed for benign thyroid diseases, such as Graves' disease, multinodular goiter, and hyperthyroidism or on autopsy of patients who had died of nonthyroid-related diseases [22–25]. However, in recent years there has been a considerable increase in the preoperative diagnosis and so in the relative rate of PMC [26–28].

The relative rate of PMC is increasing in patients with differentiated thyroid carcinoma (DTC) mainly due to more frequent use and improvement of ultrasonography and fine-needle aspiration biopsy, and also more accurate histopathological examination of surgical specimens [29]. Recently, it has been reported that papillary microcarcinomas appear to have similar biology to other papillary thyroid carcinomas [30]. These studies support that micropapillary cancer should be considered as papillary thyroid carcinoma in terms of diagnosis and treatment.

In our study, 82 patients had malignant thyroid carcinoma after surgical resection. Of these, 80 patients had well-differentiated thyroid carcinoma while 2 did not (1 medullary carcinoma, 1 anaplastic carcinoma). Forty-one of the 82 patients (50%) had tumors smaller than 1 cm. When classified according to AJCC stage, 33 patients had stage III or IV tumors, mainly due to extrathyroidal soft tissue invasion, and 10 of these tumors (30%) were smaller than 1 cm. It has been reported that 50% of thyroid carcinomas smaller than 1 cm have extrathyroidal invasion and 68% of microcarcinomas have regional lymph node metastasis [8]. Our results agree with previous studies suggesting that small nodular size does not lower the risk of malignancy or tumor invasiveness.

In previous reports, indeterminate cytology including follicular neoplasm, reflected a malignancy rate of about 20–25% [10, 31]. In our study, of 14 patients who had surgery based on indeterminate cytology, 8 were malignant (57%; 7 papillary thyroid carcinoma, 1 follicular carcinoma, 6 nodular hyperplasia). In fact, it has been demonstrated that more than 90% of well-differentiated thyroid carcinomas in Korea are papillary [32]. We did not aggressively recommend surgery when the cytologic diagnosis was indeterminate, preferring to re-examine the nodule 3 or 6 months later. This explains the low surgery rate in patients with indeterminate cytology in our study.

In summary, USgFNAC in incidental thyroid nodules revealed a high rate of malignancy. The sonographic characteristics correlated with malignancy include solid, hypoechoic, ill-defined margin, and the presence of microcalcifications. USgFNAC could be useful in detecting malignancy of thyroid nodules based on suspicious sonographic features.

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