Ultrasound-guided fine needle aspiration biopsy (FNAB) on thyroid nodules: correlation with sonographic findings

Mi-Jung Lee

Department of Medicine

The Graduate School, Yonsei University

Ultrasound-guided fine needle aspiration biopsy (FNAB) on thyroid nodules: correlation with sonographic findings

Directed by Professor **Eun-Kyung Kim**

The Master's Thesis submitted to the Department of Medicine,

the Graduate School of Yonsei University

in partial fulfillment of the requirements for the degree of

Master of Medical Science

Mi-Jung Lee

December 2006

This certifies that the Master's Thesis of Mi-Jung Lee is approved.

_____

Thesis Supervisor : Eun-Kyung Kim

_____

Woong Youn Chung

_____

Soon Won Hong

The Graduate School
Yonsei University

December 2006

ACKNOWLEDGEMENTS

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Abstract

Ultrasound-guided fine needle aspiration biopsy (FNAB) on thyroid nodules:
correlation with sonographic findings

Mi-Jung Lee

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Eun-Kyung Kim)

Purpose: To analyze the results of ultrasound-guided fine needle aspiration biopsy (FNAB) on thyroid nodules with sonographic correlation, especially for the case of insufficient or suspicious cytology results.

Methods and Materials: Total 1056 thyroid nodules of 1007 patients underwent ultrasound (US) with fine needle aspiration biopsy by one experienced radiologist in our hospital for 13 months. Diagnostic categories (benign, probably benign or suspicious) based on US findings and sonographic characterization (cyst, mixed or solid) of each nodule was prospectively evaluated. The cytology results were divided into four groups: benign, suspicious (follicular or Hurthle cell neoplasm and suspicious papillary carcinoma), malignant, and insufficient.

Results: In regard to US findings, there were 45 benign (4.3%), 765 probably benign (72.4%) and 246 suspicious (23.3%) nodules out of 1056 thyroid nodules. In sonographic characterization, 45 (4.3%) nodules were cyst, 410 (38.8%) nodules were mixed and 601 (56.9%) nodules were solid. In cytology results, 646 nodules were benign, 159 were malignant, 106 were suspicious and 145 were insufficient. Three hundred three nodules were underwent operation and in pathology results, there were 115 benign nodules and 188 malignant nodules. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and accuracy of our sonographic categories were 86.2-87.3%, 85.2-93.8%, 80.5-90.5%, 79.0-96.1% and 85.8-92.3% respectively. Sensitivity, specificity, PPV, NPV and accuracy of our FNAB cytology results were 76.8-97.3%, 66.7-99.0%, 84.5-99.3%, 69.5-93.0% and 84.5-97.2%. There were no significant differences in insufficient rates between nodules less than 1cm and more than 1cm. Among the insufficient (n=145) or suspicious (n=106) cytology results, diagnostic categories were significantly correlated with pathology results.

Conclusion: Ultrasound-guided FNAB can provide high sensitivity, specificity and

diagnostic accuracy in patients with thyroid nodules, even in small (less than 1cm) nodules. And sonographic findings are very useful in cases of insufficient or suspicious cytology results.

Key words : thyroid nodule, biopsy, ultrasound, sensitivity and specificity

Ultrasound-guided fine needle aspiration biopsy (FNAB) on thyroid nodules: correlation with sonographic findings

Mi-Jung Lee

Department of Medicine

The Graduate School, Yonsei University

Directed by Professor **Eun-Kyung Kim**

Ⅰ. INTRODUCTION

Fine needle aspiration biopsy (FNAB) is widely accepted diagnostic modality for the evaluation of thyroid nodules [1-7]. It can be done with a guidance of palpation or ultrasound (US) and several reports suggested that US-guided FNAB (US-FNAB) has many advantages over a biopsy guided by palpation [5, 8]. Real time US examination permits confirmation of the needle within the lesion, so facilitating an accurate biopsy on small non-palpable nodules. Even in palpable thyroid nodules, US-FNAB is superior to palpation-guided FNAB for obtaining adequate material as well as providing more accurate cytology evaluation [5, 9, 10].

However, there are still some limitations in US-FNAB. The major limitation is the result of insufficient or suspicious (indeterminate) aspirates. Although insufficient rate has been decreased compared with palpation-guided FNAB, that for US-FNAB has still reported about 4-40% [10, 11]. The management of nodules with insufficient or suspicious cytology is problematic in clinical situation and there are no clear guidelines for the management of these lesions [12, 13].

During or before the US-FNAB, US evaluation of thyroid nodule is performed. So US can be used not only for the guidance but also for the evaluation of thyroid nodule. With the high-resolution US equipment, there have been several reports about the US findings of thyroid nodules suggesting malignancy [14-23]. Despite there are some overlaps between benign and malignant findings, we suggest US can provide some information over the FNAB results. However, to our knowledge, there were few reports about the US-FNAB results of thyroid nodules correlated with US findings.

Our purpose of this study is to analyze the results of US- FNAB of thyroid nodules with sonographic correlation and to determine whether sonographic characterization can provide guideline for further evaluation or operation in cases with suspicious or insufficient cytology results.

Ⅱ. MATERIALS AND METHODS

From September 2002 to September 2003, total 1056 thyroid nodules in 1007 patients underwent US and US-FNAB by one experienced radiologist in our hospital. There were 935 women and 72 men with their age ranged from 12 to 82 years (mean age, 48 years). Thyroid US was performed with an HDI 3000 or 5000 scanner (Phillips, Bothell, Washington, USA) using a bandwidth of 7 to 12-MHz transducer. Before performing FNAB, US was meticulously done for characterization of the thyroid nodules. First, the size was measured as the maximal dimension and composition of the nodule (sonographic characterization) was classified as cyst, mixed or solid. Cyst means completely anechoic nodule with or without comet-tail artifact. Mixed lesion means combined solid and cystic portion.

At the time of US, each lesion was described sonographic features, including echogenecity, margin, calcifications, and shape as published our data [16]. The echogenecity was divided as hyperechogenecity, isoechogenecity, hypoechogenecity, marked hypoechogenecity, and mixed echogenecity. When the echogenecity of the nodule was similar to thyroid parenchyma, we classified it as an isoechogenecity. Marked hypoechogenicity was defined as decreased echogenicity compared with the surrounding strap muscle. The margin was divided as well circumscribed, or not-well circumscribed including microlobulated and irregular. Calcifications were divided as microcalcifications, macrocalcifications, mixed calcifications and none. Microcalcifications were defined as tiny, punctuate and hyperechoic foci either with or without acoustic shadows. Mixed calcifications were defined as combination of microcalcificaitons and macrocalcifications. Shape was assessed by the ratio of anteroposterior (A) and transverse (T) diameter (A/T≥1 or A/T<1). Mixed nodule was analyzed according to the solid portion of the nodule. Malignant sonographic features were defined as marked hypoechogenicity, not-well circumscribed margin, microcalcifications or mixed calcifications, and A/T≥1.

We prospectively classified nodules as benign, probably benign or suspicious based on US findings. If the nodule was a cyst, it was classified as benign. If any single feature suggestive of malignancy was present, it was classified as suspicious. If a nodule had no suspicious features and was not a cyst, it was classified as probably benign.

FNAB was performed by one experienced radiologist under ultrasound guidance. During the US-FNAB, patients were placed in a supine position with the neck slightly extended. After localization the lesion, the patient's neck was sterilely prepared and draped. Local anesthetic was not used during the procedure. The transducer was placed over the lesion and a 23 gauge needle attached to the 20ml syringe with syringe holder was placed just above the transducer. By watching the tip of the needle on a monitor, it was inserted almost perpendicular to the neck. The tip of the needle was clearly visible as a bright spit on the monitor. When we

targeted the mixed echoic nodule, the needle was introduced towards the solid portion of the mixed echoic lesion. When the needle reached the target, the aspiration biopsy was performed with to-and-fro movement. Suction was released before the needle was removed from the lesion. During the procedure, all the needle movements could be continuously visualized in real time. A minimum of two passes were employed. After samples were obtained, they were mounted on a glass slide and prepared for the cell block. The glass slides were fixed and stained with Papanicolaou stain. The cytology was interpreted by the cytopathologists and the cytology result was diagnosed as one of four categories: benign, suspicious (follicular or Hurthle cell neoplasm and suspicious papillary carcinoma), malignant, or insufficient. An adequate specimen was defined as containing 8-10 medium-sized fragments of follicular epithelium on at least two slides[24]. A nodule was considered benign if the specimen exhibited normal thyroid epithelial cells or thyroiditis. A follicular neoplasm was considered separately from the malignant group because it is difficult to differentiate between follicular adenoma and follicular carcinoma; therefore, the nodules classified as malignant excluded follicular carcinomas. Among the features of (1) nuclei with irregular membranes, including grooved nuclei and intranuclear cytoplasmic invaginations, (2) dense, squamoid cytoplasm and (3) evidence of papillary architecture, the presence of even one of these features is considered suspicious for malignancy[11, 25]. Nodules with suspicious or malignant cytology were referred for surgical resection and pathology results were obtained after thyroidectomy or excision operation. Then these cytology and pathology data was correlated with US categories. We calculated the sensitivity, specificity, positive predictive value, negative predictive value and accuracy for sonographic categories and FNAB results. Subgroup comparisons were statistically analyzed by chi-square tests.

Ⅲ. RESULTS

The size of 1056 thyroid nodules was ranged from 3 to 100mm (mean size, 16.6mm). Four hundred seventeen nodules (39.5%) were less than 10mm. There were no significant differences in insufficient rates between nodules less than and more than 1cm (12.5% and 15.6% respectively, p value = 0.157).

In considering of nodule composition (sonographic characterization), 45 (4.3%) nodules were cyst, 410 (38.8%) nodules were mixed and 601 (56.9%) nodules were solid. There was more inadequate cytology result in cysts (31.1%) than in mixed (13.9%) or solid (12.3%) nodules (statistics). The malignant rate was higher in solid nodules (23.6%) than in cysts (0%) or mixed nodules (4.1%) and the difference was statistically significant (p value < 0.0001) (Fig. 1).
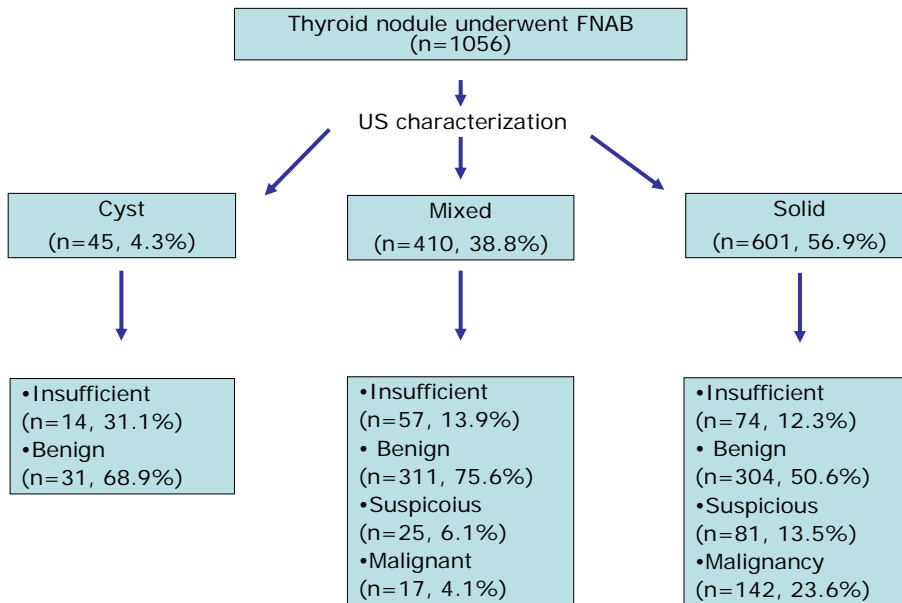
Figure 1. Diagram of thyroid nodules underwent FNAB with sonographic characterization and pathology results.

In regard to US categories, there were 45 (4.3%) benign nodules, 765 (72.4%) probably benign nodules and 246 (23.3%) suspicious nodules. The FNAB results were significantly different in benign plus probably benign group and suspicious group (p value < 0.0001). Insufficient rate was also significantly different between benign plus probably benign group and suspicious group (p value = 0.002) (Fig. 2). The sensitivity, specificity, positive

predictive value (PPV), negative predictive value (NPV) and accuracy of the sonographic categories in these cases were 86.2-87.3%, 85.2-93.8%, 80.5-90.5%, 79.0-96.1% and 85.8-92.3% according to inclusion or exclusion of FNAB only lesions.

Thyroid nodule underwent FNAB
(n=1056)
Size: 3 – 100mm

US finding

Benign
(n=45, 4.3%)

Probably Benign
(n=765, 72.4%)

Suspicious
(n=246, 23.3%)

•Insufficient
(n=14, 31.1%)
•Benign
(n=31, 68.9%)

•Insufficient
(n=106, 13.9%)
• Benign
(n=580, 75.8%)
•Suspicoius
(n=63, 8.2%)
•Malignant
(n=16, 2.1%)

•Insufficient
(n=25, 10.2%)
• Benign
(n=35, 14.2%)
•Suspicious
(n=41, 17.5%)
•Malignancy
(n=143, 58.1%)

Figure 2. Diagram of thyroid nodules underwent FNAB with sonographic categories and pathology results.

In cytology results, 646 (61.2%) nodules were benign, 159 (15.1%) were malignant, 106 (10.0%) were suspicious and 145 (13.7%) were insufficient. The sonographic categories were benign or probably benign in 94.6% of cytologically benign group (Fig. 3) and suspicious in 89.9% of cytologically malignant group (Fig. 4).

```
                    ┌─────────────────────────┐
                    │    Benign cytology      │
                    │       (n=646)           │
                    └─────────────────────────┘
                              │
                          US finding
             ┌────────────────┼────────────────┐
             ▼                ▼                 ▼
    ┌──────────────┐  ┌──────────────┐  ┌──────────────┐
    │   Benign     │  │Probably Benign│  │  Suspicious  │
    │ (n=31, 4.8%) │  │(n=580, 89.8%)│  │ (n=35, 5.4%) │
    └──────────────┘  └──────────────┘  └──────────────┘
           │                 │                 │
       Op cases          Op cases          Op cases
        (n=2)             (n=60)             (n=9)
           ▼                 ▼                 ▼
    ┌──────────────┐  ┌──────────────┐  ┌──────────────┐
    │•benign       │  │•benign       │  │•benign       │
    │(n=2)         │  │(n=57, 95%)   │  │(n=7, 77.8%)  │
    │              │  │•Malignant    │  │•Malignant    │
    │              │  │(papillary    │  │(papillary    │
    │              │  │carcinoma)    │  │carcinoma)    │
    │              │  │(n=3, 5%)     │  │(n=2, 22.2%)  │
    └──────────────┘  └──────────────┘  └──────────────┘
```
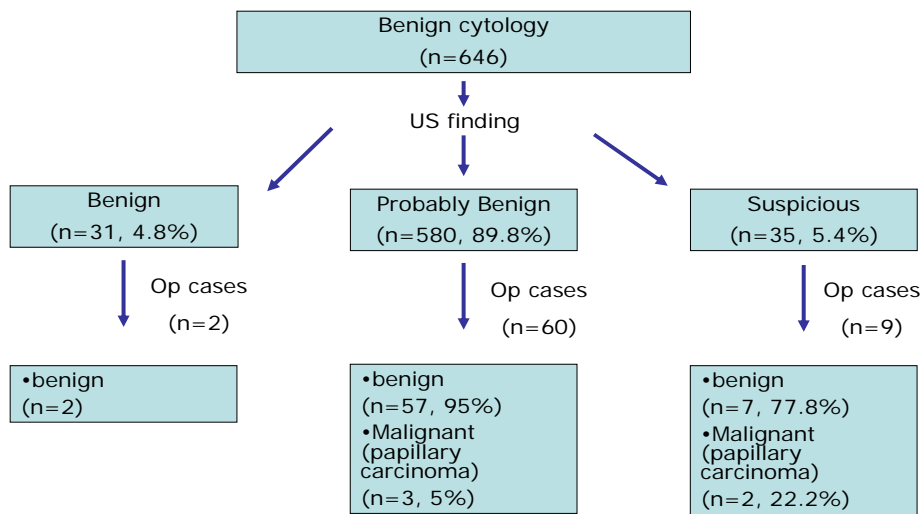
Figure 3. Diagram of benign cytology nodules with sonographic categories and pathologic results.

```
                    ┌─────────────────────────┐
                    │   Malignant cytology    │
                    │       (n=159)           │
                    └─────────────────────────┘
                              │
                          US finding
             ┌────────────────┼────────────────┐
             ▼                ▼                 ▼
    ┌──────────────┐  ┌──────────────┐  ┌──────────────┐
    │   Benign     │  │Probably Benign│  │  Suspicious  │
    │   (n=0)      │  │(n=16, 10.1%) │  │(n=143, 89.9%)│
    └──────────────┘  └──────────────┘  └──────────────┘
                             │                 │
                         Op cases          Op cases
                          (n=16)            (n=127)
                             ▼                 ▼
                      ┌──────────────┐  ┌──────────────┐
                      │•Malignant    │  │•benign       │
                      │(papillary    │  │(n=1, 0.8%)   │
                      │carcinoma)    │  │•Malignant    │
                      │(n=16)        │  │(papillary    │
                      │              │  │carcinoma 123,│
                      │              │  │other malignancy│
                      │              │  │3)            │
                      │              │  │(n=126, 99.2%)│
                      └──────────────┘  └──────────────┘
```
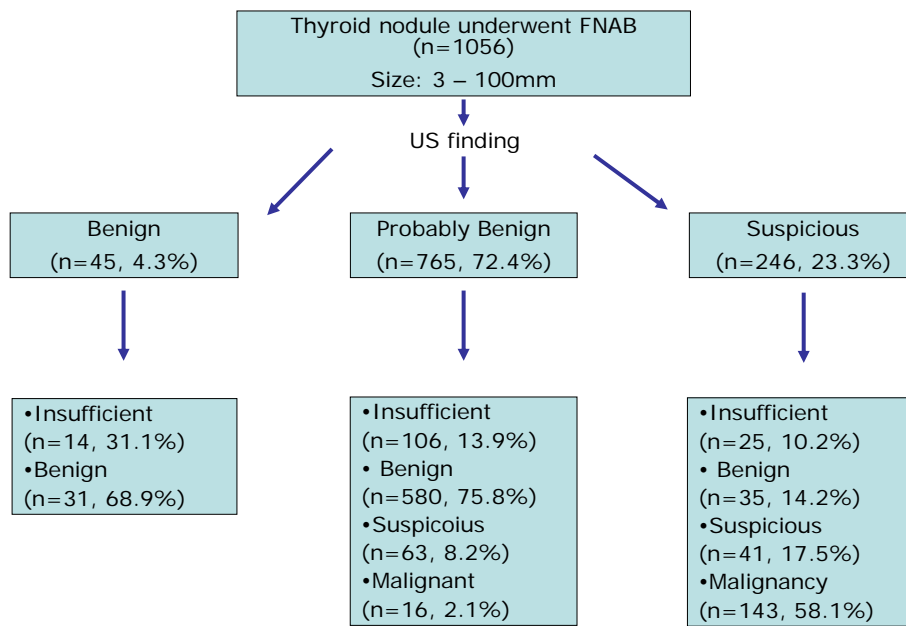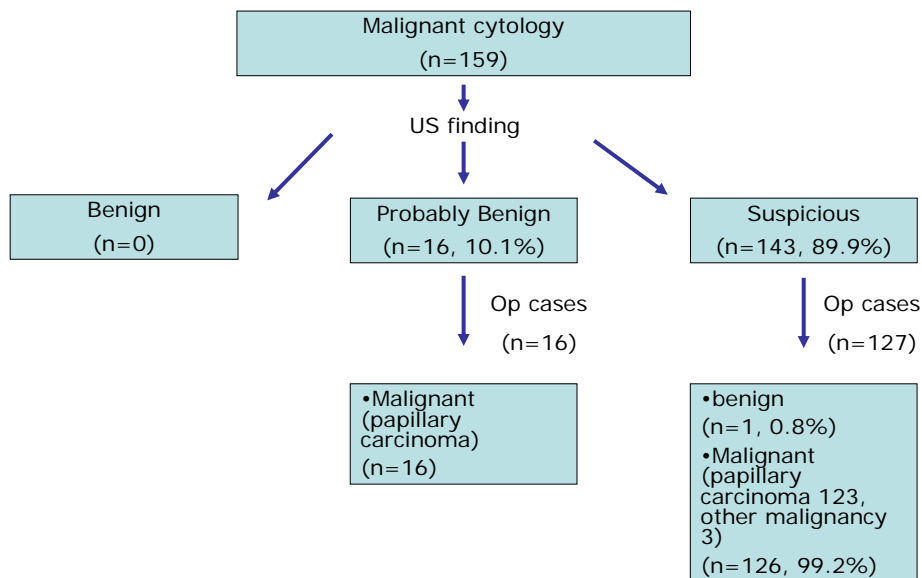
Figure 4. Diagram of malignant cytology nodules with sonographic categories and pathologic results.

Total three hundred three nodules were underwent operation and there were 115 benign and 188 malignant nodules on pathology. FNAB results according to US categories with surgical correlation are summarized in Table 1. In the diagnosis of 71 benign cytology results, 5 were turned out malignant at operation (5/71, 7.0% false negative rate). Three of them were sonographically classified as probably benign (Fig. 3). In the diagnosis of 143 malignant cytology result, only one was turned out benign at operation (1/143, 0.7% false positive rate) (Fig. 4).

Table 1. Sonographic categories and FNAB results in pathologically proven patients

diagnostic categories	FNAB result	pathologic results		
		benign(%)	malignant(%)	total
benign or probably benign nodules	benign	59(95.2)	3(4.8)	62
	malignant	0	16	16
	insufficient	10	1	11
	suspicous	29	6	35
	total	98 (79.0)	26 (21.0)	124
suspicious nodules	benign	7(77.8)	2(22.2)	9
	malignant	1	126	127
	insufficient	6	2	8
	suspicious	3	32	35
	total	17 (9.5)	162 (90.5)	179

In suspicious cytology results, there were 63 probably benign nodules and 43 suspicious nodules (Fig. 5A). Only concerned with cytology of suspicious papillary carcinoma, the sonographic categories were statistically correlated with the pathology results in this suspicious group (p value < 0.0001) (Fig. 5B). In subgroup of follicular or Hurthle cell neoplasm, sonographic categories were not different (p value = 0.823) (Fig. 5C).
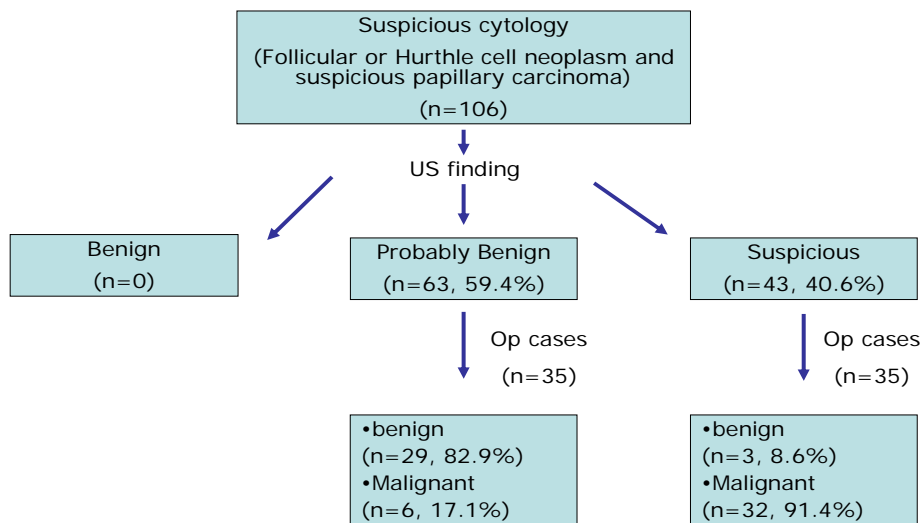
```
                    ┌─────────────────────────────────┐
                    │       Suspicious cytology       │
                    │ (Follicular or Hurthle cell     │
                    │ neoplasm and suspicious         │
                    │ papillary carcinoma)            │
                    │           (n=106)               │
                    └─────────────────────────────────┘
                                 │
                             US finding
        ┌────────────────────────┼────────────────────────┐
        ▼                        ▼                         ▼
┌───────────────┐      ┌───────────────────┐     ┌───────────────────┐
│    Benign     │      │  Probably Benign  │     │    Suspicious     │
│    (n=0)      │      │  (n=63, 59.4%)    │     │   (n=43, 40.6%)   │
└───────────────┘      └───────────────────┘     └───────────────────┘
                            │  Op cases              │  Op cases
                            ▼    (n=35)              ▼    (n=35)
                       ┌──────────────┐         ┌──────────────┐
                       │ •benign      │         │ •benign      │
                       │ (n=29,82.9%) │         │ (n=3, 8.6%)  │
                       │ •Malignant   │         │ •Malignant   │
                       │ (n=6, 17.1%) │         │ (n=32,91.4%) │
                       └──────────────┘         └──────────────┘
```

Figure 5A. Diagram of suspicous cytology nodules with sonographic categories and pathology results - suspicious cytology (both suspicious papillary carcinoma and Follicular or Hurthle cell neoplasm in cytology).
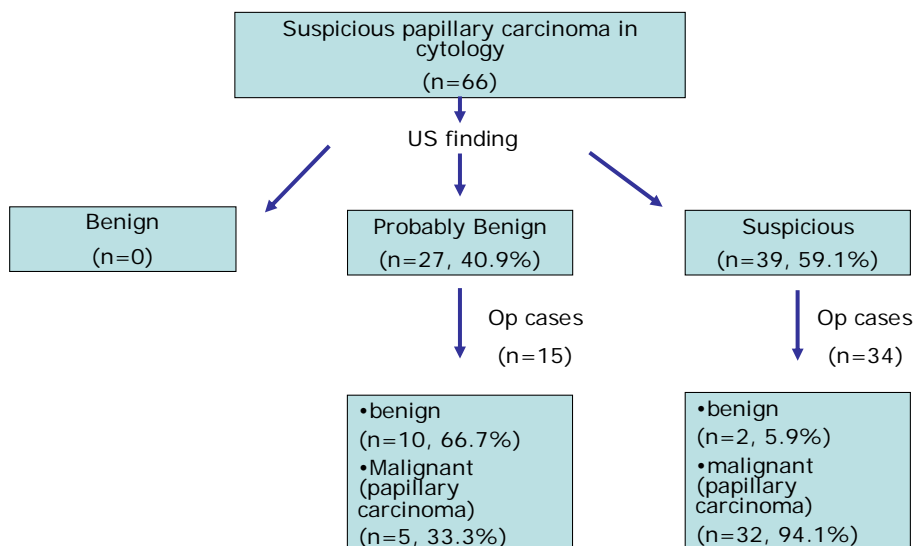
```
                    ┌─────────────────────────────────┐
                    │  Suspicious papillary carcinoma │
                    │          in cytology            │
                    │            (n=66)               │
                    └─────────────────────────────────┘
                                 │
                             US finding
        ┌────────────────────────┼────────────────────────┐
        ▼                        ▼                         ▼
┌───────────────┐      ┌───────────────────┐     ┌───────────────────┐
│    Benign     │      │  Probably Benign  │     │    Suspicious     │
│    (n=0)      │      │  (n=27, 40.9%)    │     │   (n=39, 59.1%)   │
└───────────────┘      └───────────────────┘     └───────────────────┘
                            │  Op cases              │  Op cases
                            ▼    (n=15)              ▼    (n=34)
                       ┌──────────────┐         ┌──────────────┐
                       │ •benign      │         │ •benign      │
                       │ (n=10,66.7%) │         │ (n=2, 5.9%)  │
                       │ •Malignant   │         │ •malignant   │
                       │ (papillary   │         │ (papillary   │
                       │ carcinoma)   │         │ carcinoma)   │
                       │ (n=5, 33.3%) │         │ (n=32,94.1%) │
                       └──────────────┘         └──────────────┘
```

Figure 5B. Diagram of suspicous cytology nodules with sonographic categories and pathology results - suspicious papillary carcinoma in cytology.
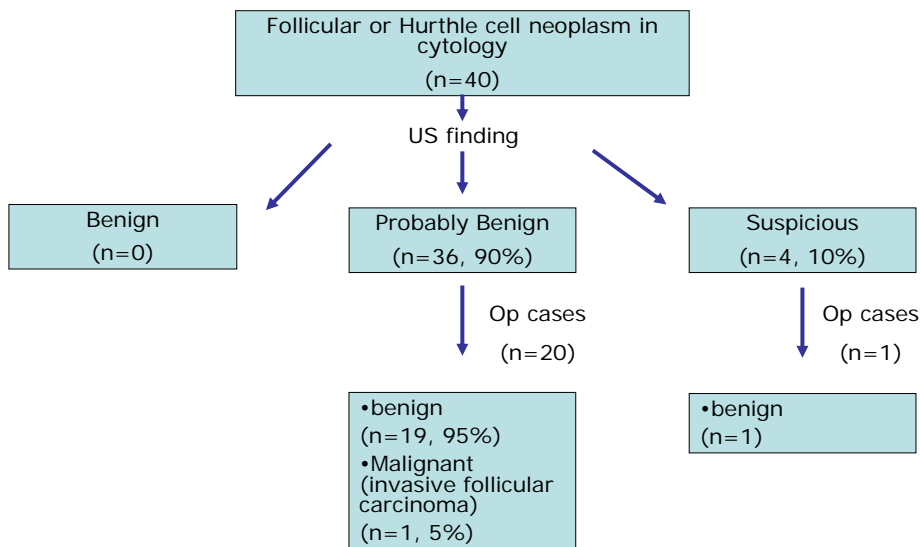
Figure 5C. Diagram of suspicous cytology nodules with sonographic categories and pathology results - Follicular or Hurthle cell neoplasm in cytology.

In insufficient cytology results, 19 nodules were operated as resulting in benign (n=16) or malignant (n=3) lesions, which showed statistical correlation between the sonographic categories and pathology results (p value = 0.035) (Fig. 6).

Sensitivity, specificity, PPV, NPV and accuracy of our FNAB cytology results were ranged 76.8-97.3%, 66.7-99.0%, 84.5-99.3%, 69.5-93.0% and 84.5-97.2% according to how to handle of insufficient or suspicious samples (Table 2).
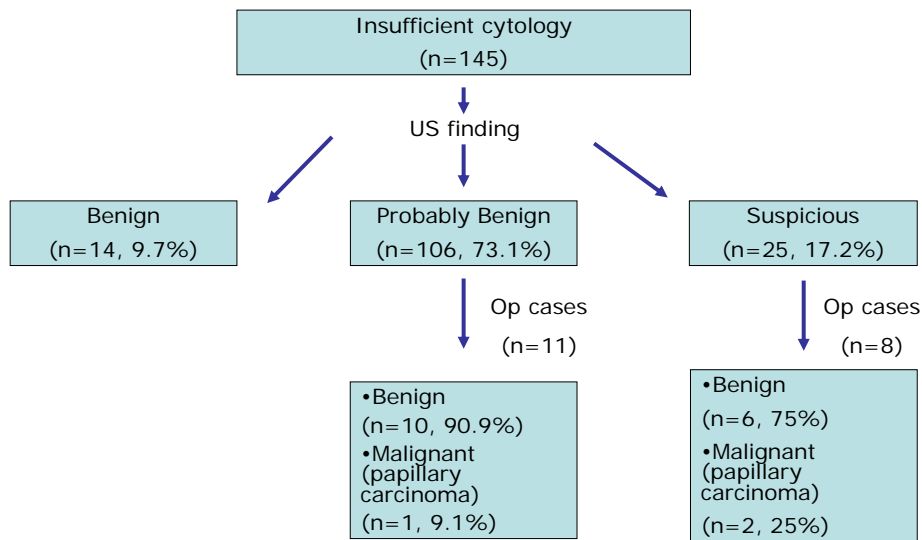
Figure 6. Diagram of insufficient cytology nodules with sonographic categories and pathology results.

Table 2. Outcome of FNAB results with variable cytology analysis

FNAB cytology results	sensitivity (%)	specificity (%)	PPV (%)	NPV (%)	accuracy (%)
only include benign and malignant cytology	142/147 (96.6)	66/67 (98.5)	142/143 (99.3)	66/71 (93.0)	208/214 (97.2)
suspicious sampes are classified as positive	180/185 (97.3)	66/99 (66.7)	180/213 (84.5)	66/71 (93.0)	246/284 (86.6)
suspicious samples are classified as negative	142/185 (76.8)	98/99 (99.0)	142/143 (99.3)	98/141 (69.5)	240/284 (84.5)
insufficient samples are classified as positive	145/150 (96.7)	66/83 (79.5)	145/162 (89.5)	66/71 (93.0)	211/233 (90.6)
insufficient samples are classified as negative	142/150 (94.7)	82/83 (98.8)	142/143 (99.3)	82/90 (91.1)	224/233 (96.1)

PPV: positive predictive value, NPV: negative predictive value

Ⅳ. DISCUSSION

Thyroid nodules are common and these increase linearly with age [26-30]. The rate of incidentally found thyroid nodules on ultrasound (US) is 30-50% [27, 30-32]. So it is important to find out clinically important nodules of malignancy. Ultrasound is useful in the diagnosis of thyroid disease, not only in terms of revealing the presence of cancer but also in identifying the most aggressive cancers [33, 34]. But it has a broad spectrum of diagnostic findings for each disease, even in thyroid cancer. The major findings that suggests malignancy include microcalcifications, irregular or microlobulated margin, marked hypoechogenicity, solid appearance, solitary nodule, taller shape and intrinsic hypervascularity [14-23]. On power Doppler images, predominantly central blood flow and high resistive index (more than 0.75) suggest malignancy [35]. But none of these characteristics is pathognomonic. For the specific diagnosis of clinically important thyroid carcinoma, there were many studies about fine-needle aspiration biopsy (FNAB) on the thyroid gland after beginning by Martin and Ellis in 1930 and FNAB is proved to be safe, inexpensive, minimally invasive, and highly accurate in the diagnosis of nodular thyroid disease, even in cystic nodules [1-7].

The statistical indices such as sensitivity, specificity, PPV, NPV and accuracy based on ultrasound are reported as 35.3-93.8%, 66-100%, 56.1%, 95.9%, and 74.8%, respectively [16, 19, 36]. Our study also shows comparable outcome of high sensitivity, specificity and accuracy in sonographic categories. But evaluating thyroid nodules, there always exist some bias because all of the thyroid nodules detected during ultrasound cannot or need not to be aspirated. Moreover, for calculating statistical indices, we evaluated not only pathology results, but also cytology results. It is because of the relatively low operation rate, especially in insufficient or benign cytology groups. Even in the cases of suspicious sonographic findings with insufficient or suspicious cytology results, only 32% (8 out of 25 nodules) and 33% (35 out of 106 nodules) were underwent operation respectively. Further evaluation such as clinical or imaging follow up of each patient is needed for the exact outcome.

FNAB shows better outcome than only ultrasonographic determination. Analysis of recent data suggests the sensitivity, specificity, false-negative rate, false-positive rate and accuracy as 65-98%, 72-100%, 1-13%, 0-23.4% and 75-88% respectively (Table 3) [3, 7, 26, 37-42]. Our study also showed good results. But the result of FNAB depends on the skill of the aspirator. Furthermore the decision can be difficult because of various sonographic findings of the thyroid nodules. Even malignant nodules of one particular histologic subtype may appear with a variety of different sonographic phenotypes, thus indicating the need for biopsy in determining further workup of thyroid nodules [19]. In view of the aspirator's skill, there is some debate about false negative and false positive rates. According to the Papanicolaous Society of Cytopathology Task

Table 3. FNAB outcomes review of previous studies

	number of nodules (or patients)	guidance method	mean size of thyroid nodules (mm)	insufficient cytology (%)	suspicious cytology (%)	sensitivity (%)	specificity (%)	PPV (%)	NPV (%)	accuracy (%)	false positive rate (%)	false negative rate (%)
Gharib et al. (1993)				17	10	65-98	72-100				1-8	1-11
Ogawa et al. (2001)	806	US	20.5	18	16	76	73	99		75		13
Mittendorf et al. (2002)	66	US	25	23							0	0
Mittendorf et al. (2002)	407	palpation	41	14							3	1.6
Sclabas et al. (2003)	(240)			5	42						4	4
Bellantone et al. (2004)	575 (534)	US	29.1	9.2	10.1	57.9-84.2	43.8-94.4			50.9-88.0		
Kessler et al. (2005)	(170)					79	98.5	98.8	76.6	87		
Blanco Carrera et al. (2005)	(510)			12.4	19	76	84					
Zagorianakou et al. (2005)	900 (900)			19.9	6.7	92.1	93.2					
Cai et al. (2006)	(434)			7.4	13.1	80.5-83.3	97.8-98.0	71.4-89.2	95.9-98.4	97.0-97.5		
Sahin et al. (2006)	327	US	18.9			98.1	63.1	35.6	99.4	69.1		
Sangalli et al. (2006)	5469 (5287)			4.1	20.2	93.4	74.9	98.6			0.2	6.2
Serna de la Saravia et al. (2006)	335			1.9-6.6	22.9-33.3	82.6-97.2						
Wu et al. (2006)	1621			10.0	15.8	87	100				0	3
our study	**1056 (1007)**	**US**	**16.6**	**13.7**	**10.0**	**76.8-97.3**	**66.7-99.0**	**84.5-99.3**	**69.5-93.0**	**84.5-97.2**	**0.7**	**7.0**

Force on Standards of Practice, a false negative rate not to exceed 2% and a false positive rate of no more than 3% are regarded as benchmarks that should be achieved on FNAB cytology of the thyroid [42]. In our study, the false positive rate was 0.7%(1/143) and the false negative rate was 7.0(5/71)% which is comparable by one experienced radiologist. Among the five false negative cases, three cases showed probably benign findings and two nodules showed suspicious findings on ultrasound.

In cytology, there is also the difficulty in distinguishing some benign cellular adenomas from their malignant counterparts, even by experienced pathologist. [1, 3, 43, 44]. The presence of psammoma bodies is associated with a specificity of 100% and a combination of nuclear grooves, micronucleoli, pseudo-inclusions, powdery chromatin, and multinucleated giant cells is also 100% specific in detecting papillary thyroid carcinoma [45]. But none of the cytology features is sufficient, so there should be suspicious or insufficient cytology results. Approximately 30% of patients with thyroid nodules have indeterminate or suspicious FNAB results. Some report that the malignancy proportion is high (about 20-30%) in these and persistent insufficient FNAB is considered an indication for surgery [26, 46-48]. So there are many suggestions about further evaluation in cell-cycle regulatory gene activity, gene mutation and molecular markers for differentiating indeterminate or suspicious cytology results [47-54]. But there are much controversial in the management with these cases even in recent reports [13]. So it is very important how to interpret these cytology results.

We showed statistically significant correlation of sonographic categories with pathology results in suspicious or insufficient cytology groups. Moreover we could calculate the statistical indices in suspicious cytology group (only suspicious papillary carcinoma, not follicular or Hurthle cell neoplasm) that showed statistically significant results. So we made an algorithm (Fig. 7) to provide useful suggestion in daily practice. In case of suspicious or insufficient cytology result with suspicious sonographic findings, malignancy cannot be excluded and repeated FNAB is needed. But in case of that with probably benign sonographic findings, US follow up is preferred. In subgroup of follicular or Hurthle cell neoplasm, sonographic categories were not correlated statistically. It may be because of small operated cases and low follicular carcinoma incidence in Korea (about 5.8% in 2002 annual report of the Korea central cancer registry). Besides the combination of ultrasound and FNAB is less effective in follicular tumor than other pathology[55].   Also we could not calculate the statistical indices in insufficient cytology group because of too small number of pathologically proven cases (only 19).
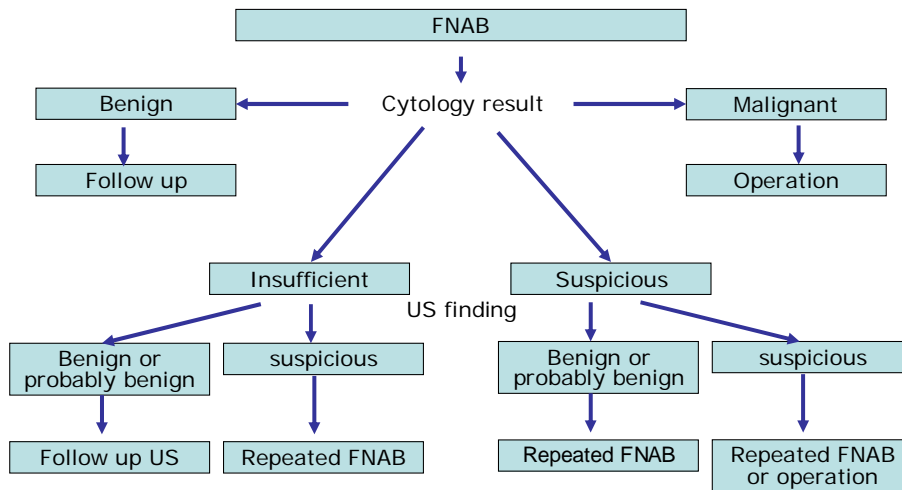
Figure 7. Algorithm for management of thyroid nodules with US-guided FNAB.

There are much debates in FNAB on specific thyroid nodules such as nonpalpable, infracentimetric nodules, multiple nodules and one nodule with repeated FNAB. Nonpalpable nodules with a size of 1.5 cm represent an absolute indication to perform an ultrasound-guided FNAB because of the malignant potential and aspiration efficacy. But the necessity of FNAB on small nodules is very controversial. About 70% of thyroid incidentaloma is smaller than 10mm and cancer prevalence is not low in the small nodules [20, 30, 55]. As Accurso A. et al.[56] reported, our study shows no significant difference in the percentage of the insufficient cytology results in the smaller (less than 10mm) thyroid nodule group. But some authors assert that it is not accurate and not cost-effective to examine all the nonpalpable thyroid nodules with ultrasound-guided FNAB and suggest that ultrasound finding can be useful in selecting the lesions to be examined cytologically by FNAB [57, 58]. In case with multiple nodules or one nodule with repeated FNAB, there are also some debates. The risk of cancer is similar in patients with solitary or multiple nodules [58]. In our study, there were 47 patients who underwent FNAB on multiple (two or three) thyroid nodules, but the number is too small to compare with single nodule group (the remaining 960 patients).

Our study has several limitations. The first limitation is that further evaluation was not included in this study, especially in benign thyroid nodules which was the majority of the study

(n=646, 61.2%). We did not investigate the follow up study or repeated FNAB results, in spite of the preference of repeated FNAB in our hospital even in benign nodules. So we cannot evaluate the efficacy of repeated FNAB. The previous reports represent variable results that repeated FNAB improves diagnostic accuracy[59, 60] or not [26, 61]. Further evaluation in a large group is needed about this issue. The second limitation is that this study was done by only one experienced radiologist in our hospital. So there is limit to generalize this result. Also further evaluation is needed in interobserver agreement study about sonographic findings.

Ⅴ. CONCLUSION

Ultrasound-guided FNAB can provide high sensitivity, specificity and diagnostic accuracy in patients with thyroid nodules, even in small nodules. And in cases of insufficient or suspicious cytology results, sonographic findings can provide useful information in determining that the further evaluation or operation is necessary or not.

REFERENCES

1.   Nguyen GK, Lee MW, Ginsberg J, Wragg T, Bilodeau D. Fine-needle aspiration of the thyroid: an overview. Cytojournal 2005;2:12.

2.   Mazzaferri EL, de los Santos ET, Rofagha-Keyhani S. Solitary thyroid nodule: diagnosis and management. Med Clin North Am 1988;72:1177-1211.

3.   Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med 1993;118:282-289.

4.   Kelly NP, Lim JC, DeJong S, Harmath C, Dudiak C, Wojcik EM. Specimen adequacy and diagnostic specificity of ultrasound-guided fine needle aspirations of nonpalpable thyroid nodules. Diagn Cytopathol 2006;34:188-190.

5.   Cesur M, Corapcioglu D, Bulut S, Gursoy A, Yilmaz AE, Erdogan N, et al. Comparison of palpation-guided fine-needle aspiration biopsy to ultrasound-guided fine-needle aspiration biopsy in the evaluation of thyroid nodules. Thyroid 2006;16:555-561.

6.   Khalid AN, Hollenbeak CS, Quraishi SA, Fan CY, Stack BC, Jr. The cost-effectiveness of iodine 131 scintigraphy, ultrasonography, and fine-needle aspiration biopsy in the initial diagnosis of solitary thyroid nodules. Arch Otolaryngol Head Neck Surg 2006;132:244-250.

7.   Bellantone R, Lombardi CP, Raffaelli M, Traini E, De Crea C, Rossi ED, et al. Management of cystic or predominantly cystic thyroid nodules: the role of ultrasound-guided fine-needle aspiration biopsy. Thyroid 2004;14:43-47.

8.   Cai XJ, Valiyaparambath N, Nixon P, Waghorn A, Giles T, Helliwell T. Ultrasound-guided fine needle aspiration cytology in the diagnosis and management of thyroid nodules. Cytopathology 2006;17:251-256.

9.   Yokozawa T, Fukata S, Kuma K, Matsuzuka F, Kobayashi A, Hirai K, et al. Thyroid cancer detected by ultrasound-guided fine-needle aspiration biopsy. World J Surg 1996;20:848-853.

10.   Mittendorf EA, Tamarkin SW, McHenry CR. The results of ultrasound-guided fine-needle aspiration biopsy for evaluation of nodular thyroid disease. Surgery 2002;132:648-654.

11.   Sangalli G, Serio G, Zampatti C, Bellotti M, Lomuscio G. Fine needle aspiration cytology of the thyroid: a comparison of 5469 cytological and final histological diagnoses. Cytopathology 2006;17:245-250.

12.   Miller B, Burkey S, Lindberg G, Snyder WH, 3rd, Nwariaku FE. Prevalence of malignancy within cytologically indeterminate thyroid nodules. Am J Surg 2004;188:459-462.

13.   Sahin M, Gursoy A, Tutuncu NB, Guvener DN. Prevalence and prediction of malignancy in cytologically indeterminate thyroid nodules. Clin Endocrinol (Oxf) 2006;65:514-518.

14.   Kang HW, No JH, Chung JH, Min YK, Lee MS, Lee MK, et al. Prevalence, clinical

and ultrasonographic characteristics of thyroid incidentalomas. Thyroid 2004;14:29-33.

15.   Atli M, Akgul M, Saryal M, Daglar G, Yasti AC, Kama NA. Thyroid incidentalomas: prediction of malignancy and management. Int Surg 2006;91:237-244.

16.   Kim EK, Park CS, Chung WY, Oh KK, Kim DI, Lee JT, et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. AJR Am J Roentgenol 2002;178:687-691.

17.   Frates MC, Benson CB, Doubilet PM, Kunreuther E, Contreras M, Cibas ES, et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab 2006;91:3411-3417.

18.   Chan BK, Desser TS, McDougall IR, Weigel RJ, Jeffrey RB, Jr. Common and uncommon sonographic features of papillary thyroid carcinoma. J Ultrasound Med 2003;22:1083-1090.

19.   Iannuccilli JD, Cronan JJ, Monchik JM. Risk for malignancy of thyroid nodules as assessed by sonographic criteria: the need for biopsy. J Ultrasound Med 2004;23:1455-1464.

20.   Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, et al. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab 2002;87:1941-1946.

21.   Cappelli C, Pirola I, Cumetti D, Micheletti L, Tironi A, Gandossi E, et al. Is the anteroposterior and transverse diameter ratio of nonpalpable thyroid nodules a sonographic criteria for recommending fine-needle aspiration cytology? Clin Endocrinol (Oxf) 2005;63:689-693.

22.   Cappelli C, Castellano M, Pirola I, Gandossi E, De Martino E, Cumetti D, et al. Thyroid nodule shape suggests malignancy. Eur J Endocrinol 2006;155:27-31.

23.   Frates MC, Benson CB, Doubilet PM, Cibas ES, Marqusee E. Can color Doppler sonography aid in the prediction of malignancy of thyroid nodules? J Ultrasound Med 2003;22:127-134.

24.   Wu HH, Jones JN, Osman J. Fine-needle aspiration cytology of the thyroid: ten years experience in a community teaching hospital. Diagn Cytopathol 2006;34:93-96.

25.   DeMay RM. The art and science of cytopathology. 2nd ed. Chicago: American Society of Clinical Pathologists; 1999.

26.   Blanco Carrera C, Garcia-Diaz JD, Maqueda Villaizan E, Martinez-Onsurbe P, Pelaez Torres N, Saavedra Vallejo P. Diagnostic efficacy of fine needle aspiration biopsy in patients with thyroid nodular disease. Analysis of 510 cases. Rev Clin Esp 2005;205:374-378.

27.   Borges-Martins L, Betea D, Thiry A, Petrossians P, Beckers A. Thyroid nodules. Rev Med Liege 2006;61:309-316.

28.   Rojeski MT, Gharib H. Nodular thyroid disease. Evaluation and management. N Engl J

Med 1985;313:428-436.

29.   Lin JD, Chao TC, Huang BY, Chen ST, Chang HY, Hsueh C. Thyroid cancer in the thyroid nodules evaluated by ultrasonography and fine-needle aspiration cytology. Thyroid 2005;15:708-717.

30.   Brander A, Viikinkoski P, Nickels J, Kivisaari L. Thyroid gland: US screening in a random adult population. Radiology 1991;181:683-687.

31.   Chung WY, Chang HS, Kim EK, Park CS. Ultrasonographic mass screening for thyroid carcinoma: a study in women scheduled to undergo a breast examination. Surg Today 2001;31:763-767.

32.   Brander A, Viikinkoski P, Nickels J, Kivisaari L. Thyroid gland: US screening in middle-aged women with no previous thyroid disease. Radiology 1989;173:507-510.

33.   Barbaro D, Simi U, Meucci G, Lapi P, Orsini P, Pasquini C. Thyroid papillary cancers: microcarcinoma and carcinoma, incidental cancers and non-incidental cancers - are they different diseases? Clin Endocrinol (Oxf) 2005;63:577-581.

34.   Braun B, Blank W. Ultrasonography of the thyroid and parathyroid gland. Internist (Berl) 2006;47:729-748.

35.   De Nicola H, Szejnfeld J, Logullo AF, Wolosker AM, Souza LR, Chiferi V, Jr. Flow pattern and vascular resistive index as predictors of malignancy risk in thyroid follicular neoplasms. J Ultrasound Med 2005;24:897-904.

36.   Levine RA. Value of Doppler ultrasonography in management of patients with follicular thyroid biopsy specimens. Endocr Pract 2006;12:270-274.

37.   Zagorianakou P, Malamou-Mitsi V, Zagorianakou N, Stefanou D, Tsatsoulis A, Agnantis NJ. The role of fine-needle aspiration biopsy in the management of patients with thyroid nodules. In Vivo 2005;19:605-609.

38.   Sakorafas GH, Peros G, Farley DR. Thyroid nodules: Does the suspicion for malignancy really justify the increased thyroidectomy rates? Surg Oncol 2006;15:43-55.

39.   Kessler A, Gavriel H, Zahav S, Vaiman M, Shlamkovitch N, Segal S, et al. Accuracy and consistency of fine-needle aspiration biopsy in the diagnosis and management of solitary thyroid nodules. Isr Med Assoc J 2005;7:371-373.

40.   Ogawa Y, Kato Y, Ikeda K, Aya M, Ogisawa K, Kitani K, et al. The value of ultrasound-guided fine-needle aspiration cytology for thyroid nodules: an assessment of its diagnostic potential and pitfalls. Surg Today 2001;31:97-101.

41.   Sclabas GM, Staerkel GA, Shapiro SE, Fornage BD, Sherman SI, Vassillopoulou-Sellin R, et al. Fine-needle aspiration of the thyroid and correlation with histopathology in a contemporary series of 240 patients. Am J Surg 2003;186:702-710.

42.   Ylagan LR, Farkas T, Dehner LP. Fine needle aspiration of the thyroid: a cytohistologic

correlation and study of discrepant cases. Thyroid 2004;14:35-41.

43.   Serna de la Saravia C, Cuellar F, Saravio Day E, Harach HR. Accuracy of aspiration cytology in thyroid cancer: a study in 1 institution. Acta Cytol 2006;50:384-387.

44.   Ersoz C, Firat P, Uguz A, Kuzey GM. Fine-needle aspiration cytology of solitary thyroid nodules: how far can we go in rendering differential cytologic diagnoses? Cancer 2004;102:302-307.

45.   Punthakee X, Palme CE, Franklin JH, Zhang I, Freeman JL, Bedard YC. Fine-needle aspiration biopsy findings suspicious for papillary thyroid carcinoma: a review of cytopathological criteria. Laryngoscope 2005;115:433-436.

46.   Fadda G, Balsamo G, Fiorino MC, Mule A, Lombardi CP, Raffaelli M, et al. Follicular thyroid lesions and risk of malignancy: a new diagnostic classification on fine-needle aspiration cytology. J Exp Clin Cancer Res 1998;17:103-107.

47.   Kebebew E, Peng M, Reiff E, Duh QY, Clark OH, McMillan A. ECM1 and TMPRSS4 are diagnostic markers of malignant thyroid neoplasms and improve the accuracy of fine needle aspiration biopsy. Ann Surg 2005;242:353-363.

48.   Kebebew E, Peng M, Reiff E, Duh QY, Clark OH, McMillan A. Diagnostic and prognostic value of cell-cycle regulatory genes in malignant thyroid neoplasms. World J Surg 2006;30:767-774.

49.   Carpi A, Naccarato AG, Iervasi G, Nicolini A, Bevilacqua G, Viacava P, et al. Large needle aspiration biopsy and galectin-3 determination in selected thyroid nodules with indeterminate FNA-cytology. Br J Cancer 2006;95:204-209.

50.   Jin L, Sebo TJ, Nakamura N, Qian X, Oliveira A, Majerus JA, et al. BRAF mutation analysis in fine needle aspiration (FNA) cytology of the thyroid. Diagn Mol Pathol 2006;15:136-143.

51.   Lerma E, Mora J. Telomerase activity in "suspicious" thyroid cytology. Cancer 2005;105:492-497.

52.   Letsas KP, Andrikoula M, Tsatsoulis A. Fine needle aspiration biopsy-RT-PCR molecular analysis of thyroid nodules: a useful preoperative diagnostic tool. Minerva Endocrinol 2006;31:179-182.

53.   Cerutti JM, Latini FR, Nakabashi C, Delcelo R, Andrade VP, Amadei MJ, et al. Diagnosis of suspicious thyroid nodules using four protein biomarkers. Clin Cancer Res 2006;12 (Pt 1):3311-3318.

54.   Rowe LRM, Bentz BGM, Bentz JSM. Utility of BRAF V600E mutation detection in cytologically indeterminate thyroid nodules. Cytojournal 2006;3:10.

55.   Nam-Goong IS, Kim HY, Gong G, Lee HK, Hong SJ, Kim WB, et al. Ultrasonography-guided fine-needle aspiration of thyroid incidentaloma: correlation with

pathological findings. Clin Endocrinol (Oxf) 2004;60:21-28.

56.   Accurso A, Rocco N, Palumbo A, Leone F. Usefulness of ultrasound-guided fine-needle aspiration cytology in the diagnosis of non-palpable small thyroid nodules. Tumori 2005;91:355-357.

57.   Carpi A, Nicolini A, Casara D, Rubello D, Rosa Pelizzo M. Nonpalpable thyroid carcinoma: clinical controversies on preoperative selection. Am J Clin Oncol 2003;26:232-235.

58.   Lansford CD, Teknos TN. Evaluation of the thyroid nodule. Cancer Control 2006;13:89-98.

59.   Furlan JC, Bedard YC, Rosen IB. Single versus sequential fine-needle aspiration biopsy in the management of thyroid nodular disease. Can J Surg 2005;48:12-18.

60.   Orlandi A, Puscar A, Capriata E, Fideleff H. Repeated fine-needle aspiration of the thyroid in benign nodular thyroid disease: critical evaluation of long-term follow-up. Thyroid 2005;15:274-278.

61.   Shin JH, Han BK, Ko K, Choe YH, Oh YL. Value of repeat ultrasound-guided fine-needle aspiration in nodules with benign cytological diagnosis. Acta Radiol 2006;47:469-473.

Abstract (in Korean)

갑상선 결절에 대한 초음파 유도 하 세침 흡입 검사:
초음파 소견과의 상관

<지도교수 김 은 경>

연세대학교 대학원 의학과
이 미 정

이 논문의 목적은 갑상선 결절에 대한 초음파 유도 하 세침 흡입 검사의 결과를 초음파 소견과 상관하여 분석하기 위한 것이다. 특히 세포검사 결과가 불충분(insufficient) 또는 의심(suspicious)으로 나온 경우 초음파 소견의 의미를 알아보고자 하였다.

분석 대상은 지난 13개월 간 우리 병원에서 한 명의 숙련된 방사선과 전문의가 초음파 유도 하 세침 흡입 검사를 시행한 환자들이었다. 이 환자들은 모두 1007명이었고, 시행 받은 갑상선 결절의 수는 1056개였다. 전향적으로 초음파 소견에 따른 진단 범주를 양성, 대개 양성 또는 의심으로 나누었고, 각각의 갑상선 결절의 특성을 액체, 고체 또는 혼합으로 분류하여 평가하였다. 세포검사 결과는 양성, 의심 (여포 종양 또는 허틀씨 세포암, 그리고 유두암 의심), 악성 그리고 불충분의 네 범주로 나누었다.

초음파 소견상 전체 1056 갑상선 결절 중 45개(4.3%)가 양성, 765개(72.4%)가 대개 양성 그리고 246개(23.3%)가 의심으로 나왔다. 갑상선 결절의 특성은 45개(4.3%)가 액체, 601개(56.9%)가 고체 그리고 410개(38.8%)가 혼합으로 나왔다. 세포검사 결과는 646개가 양성, 159개가 악성, 106개가 의심 그리고 145개가 불충분으로 나왔다. 이 중 303개의 결절에 대하여 수술이 시행되었고, 병리검사 결과 115개가 양성, 188개가 악성 결절로 밝혀졌다. 초음파 진단 범주의 민감도, 특이도, 양성 예측률, 음성 예측률 그리고 정확도는 각각 86.2-87.3%, 85.2-93.8%, 80.5-90.5%, 79.0-96.1% 그리고 85.8-92.3%였다. 세침 흡입 검사의 민감도, 특이도, 양성 예측률, 음성 예측률 그리고 정확도는 각각 76.8-97.3%, 66.7-99.0%, 84.5-99.3%, 69.5-93.0% 그리고 84.5-97.2%였다. 세포검사 결과가 불충분으로 나온 비율은 결절의 크기(1cm 기준)와 큰 상관관계를 보이지 않았다. 세포검사 결과가 불충분(145개) 또는 의심(106개)으로 나온 경우, 초음파 진단 범주가 병리검사 결과와 유의한 상관관계를 보였다.

결론적으로 갑상선 결절의 초음파 유도 하 세침 흡입 검사는 작은 결절(1cm 이하)에 있어서도 높은 민감도, 특이도 그리고 정확도를 보이며, 특히 세포검

사 결과가 불충분 또는 의심으로 나온 경우 초음파 소견은 매우 유용한 정보를 제
공한다.

핵심되는 말 : 갑상선 결절, 생체 검사, 초음파, 민감도와 특이도