Clinicopathological characteristics of thyroid cancer misdiagnosed by fine needle aspiration

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Abstract. Fine-needle aspiration (FNA) is commonly used as a preoperative assessment to diagnose thyroid cancer. However, misdiagnosis of malignancy by FNA is not rare, even if image examination suggests the possibility of thyroid cancer. In the present study, the clinicopathological factors of patients whose preoperative FNA examination had not led to a diagnosis of thyroid cancer were examined. In total, 125 patients with thyroid cancer who underwent FNA and surgery (total thyroidectomy, subtotal thyroidectomy or hemithyroidectomy) at the Department of Surgery, Surgical Oncology and Science of the Sapporo Medical University Hospital between 2006 and 2013 were retrospectively analyzed. The patients were divided into two groups: Group A, malignancy determined by FNA, and group B, no malignancy. The groups were then compared by gender, age, tumor size, stage, tumor stage, lymph node metastasis, histology, surgical procedure methods, presence or absence of calcification and thyroglobulin levels. The mean age of the patients in group A (5 males and 59 females) was 53.0 years. The mean age in group B (11 males and 49 females) was 54.2 years. The mean tumor size in both groups was 1.6 cm. The mean thyroglobulin levels were 82.7 ng/ml in Group A and 525.5 ng/ml in group B. There were also significant differences between the groups for tumor stage (P=0.046), histological type (P=0.024) and thyroglobulin levels (P=0.035). The results of the present study suggested that it may be difficult to diagnose thyroid cancer by FNA in cases with non-papillary carcinoma and higher thyroglobulin levels.

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Introduction

Fine-needle aspiration (FNA) is the most commonly used method for the preoperative assessment of thyroid nodules. FNA provides important information with regard to the most suitable surgical treatment, and the routine use of FNA has reduced the number of unnecessary surgical procedures for thyroid nodules. The American Thyroid Association guidelines state that FNA should be used as one of the initial diagnostic tests due to its high diagnostic reliability and cost-effectiveness. However, false-negative rates are generally reported to be 3.6-10.2% (1-4). The method provides diagnostically useful results in ~80% of cases, and its sensitivity and specificity have been reported to be 83 and 92%, respectively (5). In the present study, the clinicopathological characteristics of thyroid cancers that were misdiagnosed by FNA were compared and a retrospective follow-up study of the patients who underwent surgery for thyroid cancer was performed.

Patients and methods

Patients. A total of 125 patients with thyroid cancer treated at the Department of Surgery, Surgical Oncology and Science of the Sapporo Medical University Hospital (Sapporo, Japan) between April 2006 and April 2013 were retrospectively analyzed in the present study. Patients with thyroid cancer were eligible for inclusion in the present study if they had been treated with total thyroidectomy, subtotal thyroidectomy or hemithyroidectomy. The patients who underwent FNA and surgical treatment had been pathologically diagnosed with thyroid cancer using general rules for the description of thyroid tumors (6). All FNAs had been performed with the guidance of ultrasound, using a 22G needle attached to a 20 ml disposable plastic syringe and aspirator with hand-free techniques.

The present study was performed according to the Ethical Guidelines for Clinical Research of the Japanese Ministry of Health, Labor and Welfare. An independent ethics committee for each participating site approved the protocol and any modifications. Written informed consent was obtained from all patients or the patient's family.

Experiments. Thyroglobulin levels were measured using an electrochemiluminescence assay (Elecsys® Tg II, Roche Diagnostics International AG, Rotkreuz, Switzerland), and calcification within the thyroid gland was detected using ultrasonography or computed tomography. The clinical information of the patients obtained from their medical records is presented in Table I. Smears had been fixed in 95% methanol while still wet and stained using standard Papanicolaou stains. The presence or absence of calcification (both micro and macro) had been determined by ultrasonography or computed tomography.

Groups. The patients were divided into two groups according to the Papanicolaou Society of Cytopathology classification system for FNA specimens: Group A (n=64) contained patients diagnosed with thyroid cancer by FNA, and group B (n=61) consisted of the patients with no malignancy, as determined by FNA.

Statistical analyses. The clinicopathological characteristics of thyroid cancer in both groups were retrospectively analyzed using SAS 9.4 software (SAS Institute, Tokyo, Japan). Comparisons of clinicopathological characteristics between the different subgroups were performed using an independent-samples t-test and χ^2 test. Variables with statistical significance in the univariate analysis were investigated by multivariate analysis. In addition, odds ratios and 95% confidence intervals were estimated. All P-values were two-sided and considered statistically significant if <0.05.

Results

Patient demographics. The characteristics of the 125 patients who received surgical treatment for thyroid cancer are presented in Table I. The mean ages of the patients in groups A and B were 53.0 and 54.2 years, respectively. Group A included 5 males and 59 females, and group B included 11 males and 49 females. Women were therefore predominant in both groups.

Postoperative pathological characteristics. Papillary carcinoma was the primary histological type identified, accounting for the majority of patients in both groups (62 patients in group A and 50 patients in group B). The characteristics of the patients (age, gender, tumor size, tumor stage, lymph node metastasis, histology, surgical method, calcification and thyroglobulin levels) in groups A and B were analyzed using a χ^2 test. Statistically significant differences between the two groups were observed for stage (P=0.046), histology (P=0.024) and mean thyroglobulin levels (P=0.035).

Similarly, when the patients were divided into two subgroups according to the presence or absence of calcification, a significant difference was observed between the two subgroups only for gender (Table II).

The thyroglobulin levels were also analyzed by dividing the patients into two subgroups (Table III). Significant statistical differences were observed between the two groups for stage (P=0.008), tumor size (P=0.025), histology (P=0.004) and surgical methods (P=0.009). Independent-samples t-tests were performed to compare the patients of group A with those of group B (Table IV), patients with calcification and patients without calcification (Table V), and patients with thyroglobulin levels ≥100 and those with thyroglobulin levels <100 (Table VI).

Significant differences were observed in the preoperative thyroglobulin levels between patients of group A and patients of group B, in age between the patients with calcification with calcification and those without, and in tumor size between patients with preoperative thyroglobulin levels ≥100 ng/ml and those with preoperative thyroglobulin levels <100 ng/ml.

Multivariate logistic regression analysis was performed using tumor stage, histology and thyroglobulin levels as variables in groups A and B (Table VII). Histologies other than papillary carcinoma (follicular and poorly differentiated carcinoma) and preoperative serum thyroglobulin levels of ≥100 ng/ml were significant factors when FNA cytology did not provide evidence for malignancy.

Discussion

The high incidence of thyroid nodules has been well-established. Thyroid nodules can be discovered by ultrasonography in over half of all patients, even if the sizes of the nodules are small (7). Patients frequently detect the nodule themselves by noticing a neck mass, and the nodules can also be detected by cervical palpation in a health checkup, or by chest computed tomography performed for the assessment of diseases other than thyroid diseases (8). Furthermore, the frequency of carotid ultrasonography as a routine examination to search for arteriosclerosis is now increasing, and thus small and/or clinically insignificant thyroid nodules are also incidentally detected (9).

When an ultrasonography reveals the presence of thyroid nodules, FNA cytology is often performed (10). However, performing FNA cytology for all nodules is impractical. At the Department of Surgery, Surgical Oncology and Science of the Sapporo Medical University Hospital a 'wait-and-see' strategy is applied for cases of thyroid nodules measuring ≤5 mm in diameter, those measuring 6-10 mm that appear benign on ultrasound, and those measuring 11-20 mm that are apparently cysts. Therefore, nodules that should be targeted for cytology include those measuring 6-10 mm that are suspected cases of papillary carcinoma, those measuring 11-20 mm that are suspected of being solid masses, and those measuring ≥21 mm.

Papillary carcinoma, which is easy to diagnose on ultrasound, accounts for 90% of all cases of thyroid cancer (11). The ultrasound features of typical papillary carcinoma include an irregular shape, ill-defined margins, a low echoic content, and frequent minute calcification inside the carcinoma (12,13). However, as some papillary carcinomas have a regular shape and are difficult to differentiate from follicular tumors and adenomatous goiter, caution is required (14). In those cases, FNA has the advantage that it can easily be repeated if necessary (13). A previous study reported that it may be advantageous to perform repeated procedures (15). During FNA, a low echoic portion of the irregular inner echoic content is targeted, and a tissue sample is cut with a needle tip and removed by suction in order to obtain a cell mass (16). It has been reported that 92.5% of thyroid cancers are papillary cancer in Japan (17). Therefore, if thyroid nodules are diagnosed by FNA cytology to be malignant or are suspected of being malignant, they are

Table I. Comparison of the cytology results.

	Group A		Group B		
Variable	Number (mean)	SD (%)	Number (mean)	SD (%)	P-value
Age (years)	53.0	14.3	54.2	17.3	0.669
Gender					
Male	5	7.8	11	18.3	0.081
Female	59	92.2	49	81.7	
Tumor size (cm)	1.6	0.7	1.6	1.1	0.754
Stage					
I	30	46.9	31	52.5	0.046
II	1	1.6	1	1.7	
III	20	31.2	18	30.5	
IVA	13	20.3	4	6.8	
IVC	0	0.0	5	8.5	
Tumor stage					
T1a	16	25.0	20	33.3	0.218
T1b	18	28.1	10	16.7	
T2	8	12.5	4	6.7	
T3	21	32.8	22	36.7	
T4a	1	1.6	4	6.7	
Lymph node metastasis					
N0	19	29.7	25	41.7	0.306
N1a	25	39.1	22	36.7	
N1b	20	31.2	10	16.7	
NX	0	0.0	3	5.0	
Histology					
Papillary	62	96.9	50	82.0	0.024
Follicular	1	1.6	6	9.8	
Poorly	1	1.6	5	8.2	
Operation methods					
Hemi-Tx	23	35.9	19	31.7	0.86
Subtotal-Tx	17	26.6	18	30.0	
Total-Tx	24	37.5	23	38.3	
Calcification					
+	25	39.7	17	27.9	0.165
-	38	60.3	44	72.1	
Thyroglobulin (ng/ml)	82.7	284.3	525.5	1626.1	0.035

Tx, Thyroidectomy; SD, standard deviation.

usually diagnosed as papillary carcinoma. When patients are suspected of having papillary carcinoma, they are regarded as candidates for surgery (18).

Thyroglobulin is a thyroid-specific protein secreted by the thyroid follicles. Papillary and follicular carcinoma cells also produce thyroglobulin (19). However, thyroglobulin is also secreted by follicular adenoma and adenomatous goiter, which are benign diseases, and serum levels of thyroglobulin are also elevated in Basedow's and Hashimoto's diseases (20). Therefore, serum thyroglobulin levels cannot be used to reliably differentiate between benign and malignant lesions (21). Guidelines for the treatment of thyroid tumors include similar treatments to those used for nodular goiter (22). The guidelines describe abnormally high serum levels of thyroglobulin (≥1,000 ng/ml) as a surgical indication established by consensus of the guideline committee. When there is no recurrence of the tumor following total thyroidectomy, thyroglobulin levels decrease below detectable levels (23). Therefore, thyroglobulin is a useful marker for the recurrence of differentiated thyroid cancer.

In the present study, the clinicopathological factors of patients for whom preoperative FNA cytology did not provide evidence of malignancy were examined. The results revealed

Table II. Comparison of the presence or absence of thyroid calcification.

	Calcification (+)		Calcification (-)		
Variable	Number (mean)	SD (%)	Number (mean)	SD (%)	P-value
Gender					
Male	15	16.7	1	2.2	0.010
Female	68	83.3	44	97.8	
Stage					
I	36	43.9	26	57.8	0.202
II	1	1.2	1	2.2	
III	27	32.9	11	24.4	
IVA	11	13.4	7	15.6	
IVC	7	8.5	0	0.0	
Tumor stage					
T1a	24	28.9	14	31.1	0.796
T1b	16	19.3	12	26.7	
T2	10	12.1	4	8.9	
T3	29	34.9	14	31.1	
T4a	4	4.8	1	2.2	
Tumor size (cm)					
<1.0	21	25.0	12	26.7	0.565
1.0~1.9	35	41.7	22	48.9	
≧2.0	28	33.3	11	24.4	
Lymph node metastasis					
N0	29	34.9	18	40.0	0.852
N1a	32	38.6	16	35.6	
N1b	20	24.1	10	22.2	
NX	2	2.4	1	2.2	
Histology					
Papillary	72	85.7	42	93.3	0.398
Follicular	6	7.1	2	4.4	
Poorly	6	7.1	1	2.2	
Operation methods					
Hemi-Tx	24	28.9	20	44.4	0.103
Subtotal-Tx	22	26.5	13	28.9	
Total-Tx	37	44.6	12	26.7	
Thyroglobulin (ng/ml)					
<50.0	44	53.7	28	62.2	0.578
50.0-99.9	13	15.8	7	15.7	
≧100.0	25	30.5	10	22.2	

Tx, Thyroidectomy; SD, standard deviation.

that histology other than papillary carcinoma (follicular and poorly differentiated carcinoma) and preoperative thyroglobulin levels of ≥100 ng/ml were significant factors in misdiagnosis by FNA. Kitagawa *et al* (21) reported that, according to the FNA classification, cytology specimens were 'malignant' in 99.7% of specimens, 'suspected of malignancy' in 93.3%, 'indeterminate' in 42.4%, 'benign' in 8.8% and 'inadequate' in 33.3%. The authors also described the association between the FNA classification and histopathological diagnosis confirmed by surgery (21). A total of 44 specimens were diagnosed as benign by cytology and malignant by histopathology, and 24/44 specimens (54.5%) were identified as follicular carcinoma (24,25).

In this study, the patients were classified according to the Papanicolaou Society of Cytopathology classification system for FNA samples into group A, including only patients with 'malignant' specimens, and group B, including only patients with specimens that were 'suspected of malignancy,' 'indeterminate,' 'normal or benign,' or 'inadequate.' Of the 112 patients

Table III. Comparison of the preoperative thyroglobulin levels.

	Thyroglobulin ≥100 ng/ml		Thyroglobulin <100 ng/ml		
Variable	Number (mean)	SD (%)	Number (mean)	SD (%)	P-value
Gender					
Male	4	11.4	11	11.7	0.966
Female	31	88.6	83	88.3	
Stage					
I	16	45.7	48	51.6	0.008
II	0	0.0	2	2.2	
III	10	28.6	28	30.1	
IVA	3	8.6	14	15.0	
IVC	6	17.1	1	1.1	
Tumor stage					
T1a	8	22.9	30	31.9	0.089
T1b	4	11.4	25	26.6	
T2	7	20.0	7	7.5	
T3	14	40.0	29	30.8	
T4a	2	5.7	3	3.2	
Tumor size (cm)					
<1.0	8	22.9	25	26.6	0.025
1.0~1.9	10	28.6	46	48.9	
≥2.0	17	48.6	23	24.5	
Lymph node metastasis					
N0	16	45.7	31	33.0	0.324
N1a	10	28.6	39	41.5	
N1b	9	25.7	21	22.3	
NX	0	0.0	3	3.2	
Histology					
Papillary	26	74.3	88	93.6	0.004
Follicular	6	17.1	2	2.1	
Poorly	3	8.6	4	4.3	
Operation methods					
Hemi-Tx	9	35.9	35	37.2	0.009
Subtotal-Tx	5	26.6	30	31.9	
Total-Tx	21	37.5	29	30.9	
FNA					
Others	23	71.9	37	40.7	0.002
ClassV	9	28.1	54	59.3	
Calcification					
-	10	28.6	35	38.0	0.319
+	25	71.4	57	62.0	

Tx, Thyroidectomy; SD, standard deviation.

with papillary carcinoma, 62 had been diagnosed as having malignant lesions by cytology.

For other histological types, 1/7 patients with follicular carcinoma and 1/6 patients with anaplastic carcinoma were diagnosed with malignant lesions by cytology; and therefore the diagnostic accuracy was low. Papillary carcinoma is a malignant tumor derived from the follicular epithelium and well-differentiated adenocarcinoma with a basically papillary structure (26). Papillary carcinoma has numerous cytological features including overlapping nuclei, ground glass nuclei, nuclear grooves, and intranuclear cytoplasmic inclusions in the cancer cell nuclei that provide diagnostic evidence; thus, the diagnostic accuracy for this type of carcinoma is high (27). However, cytological abnormalities of endocrine tumors,

Table IV. Comparison of patients with malignancy and those without (t-test results).

		Group A		Group B		
Variable	Group A/Group B	Mean	SD (%)	Mean	SD (%)	P-value
Age (years)	64/60	53.0	14.3	54.2	17.3	0.669
Tumor size (cm)	64/61	1.6	0.7	1.6	1.1	0.754
Thyroglobulin (ng/ml)	63/60	82.7	284.3	525.5	1,626.1	0.035

SD, standard deviation.

Table V. Comparison of patients with calcification and those without (t-test results).

		Calcification (+)		Calcification (-)		
Variable	(+)/(-)	Mean	SD (%)	Mean	SD (%)	P-value
Age (years)	83/45	56.3	15.9	50.2	2.3	0.039
Tumor size (cm)	84/45	1.7	1.5	1.5	1.2	0.305
Thyroglobulin (ng/ml)	82/45	880.1	3,884.9	274.9	1,152.8	0.310

SD, standard deviation.

Table VI. Comparison of patients with high thyroglobulin levels and those with low thyroglobulin levels (t-test results).

		Thyroglobulin ≧100		Thyroglobulin <100		
Variable	≧100/<100	Mean	SD (%)	Mean	SD (%)	P-value
Age (years)	35/94	56.8	16.6	52.7	15.6	0.195
Tumor size (cm)	35/94	2.1	1.5	1.4	0.7	0.001

SD, standard deviation.

including thyroid cancer, are generally mild and the findings for malignant and benign cells overlap (28).

When there is a discrepancy between the cytological findings and clinical diagnosis, cytological underdiagnosis appears to be likely (29). Therefore, with the exception of patients with papillary carcinoma, which is easily diagnosed, it is speculated that numerous patients received a false negative diagnosis in which cancer was erroneously classified as benign.

In the present study, the patients were examined according to thyroglobulin levels and classified either as thyroglobulin levels of 50, 50-100, or ≥100 ng/ml. As for the distribution of thyroglobulin levels, the median was 37.0 ng/ml, and the mean was 656.3 ng/ml. The patients were divided into three groups for analysis. Patients with high thyroglobulin levels may have had pathological conditions causing thyroglobulin elevation, such as chronic thyroiditis, as the background of resected thyroid glands. Lee *et al* (30) reported that papillary carcinoma was significantly associated with pathologically confirmed chronic thyroiditis. However, further studies are required in order to investigate this possibility.

Table VII. Multivariate analysis of tumor stage, histological type and thyroglobulin levels.

Variable	OR	95% CI	P-value
Stage			
I	1.00		
II or III	1.36	0.58-3.20	0.486
IVA or IVC	2.70	0.77-9.43	0.120
P for trend, P=0.220			
Histology			
Papillary	1.00		
Non-papillary	0.13	0.03-0.68	0.015
Thyroglobulin (ng/ml)			
<50.0	1.00		
50.0-99.9	0.45	0.16-1.32	0.147
≧100.0	0.26	0.10-0.69	0.007

SD, standard deviation; OR, odds ratio; CI, confidence interval.

In conclusion, for the differential diagnosis of thyroid masses, FNA cytology is an essential diagnostic procedure and provides important information which regards to the suitability of surgical treatment. As cases with thyroid masses other than those with papillary carcinoma are often difficult to diagnose by cytology, these masses should be comprehensively assessed based on the combined results of both cytological and image diagnoses.

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