Correlation of Ultrasonography with Fine Needle Aspiration Cytology and Final Pathological Diagnoses in Patients with Thyroid Nodules

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The aim of this study was to evaluate the relationship of the combined use of ultrasonography (US) and fine needle aspiration cytology (FNAC) with final pathological results in patients with thyroid nodules.

We retrospectively reviewed data from 1,725 patients who had received US examination at our institution between January 2006 and February 2008. Of these patients, 102 (5.9%) had undergone surgical treatment, 90 of whom were also examined by FNAC. The results of FNAC were categorized into 4 groups: malignant, benign, indeterminate and unsatisfactory. We then evaluated the correlations between diagnosis and thyroid US, FNAC, and final pathological results.

The age of the 102 patients who received surgery ranged from 13 to 79 years (mean age, 45.5 ± 15.3 years). The female: male ratio was 5.4:1. Seventy-eight patients were diagnosed as having benign lesions (76.5%) and 24 patients as having a malignancy (23.5%), including 20 papillary cancers, 1 anaplastic cancer, 1 medullary cancer and 2 metastatic cancers. Ninety patients received FNAC after US. The positive predictive value for detection of malignancy using FNAC was 94.7% (18/19 cases) and the negative predictive value was 93% (66/71 cases). The sensitivity of the cytological diagnosis was 78.3% (18/23 cases) and the specificity was 98.5% (66/67 cases). The overall positive predictive value for malignancy using both thyroid US and FNAC was 94.7% (18/19 cases) and the negative predictive value, 92.8% (77/83 cases). The sensitivity of the combined investigations was 75% (18/24 cases) and the specificity, 98.7% (77/78 cases). Of the 16 indeterminate cytological cases, 3 were diagnosed as having a malignant lesion (18.7%). In patients with cystic lesions, 4.7% of cases (1/21 cases) were diagnosed as malignant. One patient with a papillary microcarcinoma with neck lymph node metastasis had only a tiny calcified spot in the parenchyma of the thyroid.

US with FNAC is useful in the initial evaluation of thyroid nodules. Surgical treatment should be considered for indeterminate cases. It is also important to pay attention to microcalcification in diffuse goiters, especially in patients with neck lymph node enlargement.
in females and 19% in males) [1]. Since most thyroid nodules are benign, it is important to categorize these nodules as either benign or malignant lesions before thyroid surgery [2]. Early detection of thyroid cancer is important since it leads to better prognosis and the detected lesions are at a less advanced clinical stage [3]. Ultrasonography (US) is a convenient tool for detecting thyroid nodules [4]. Fine needle aspiration cytology (FNAC) is also performed routinely as an outpatient procedure since this procedure has better diagnostic accuracy than free hand palpation. Combined application of US and FNAC may therefore aid in detecting the majority of thyroid cancers undetected by routine clinical examination [5].

The purpose of this study was to investigate the correlation between combined US and FNAC and final pathological results in patients with thyroid nodules and to assess the contribution of FNAC in the diagnosis of thyroid cancer.

**MATERIALS AND METHODS**

In this study, we retrospectively evaluated 1,725 patients who had undergone thyroid US investigations performed by endocrinologists at an outpatient clinic at our institution between January, 2006 and February, 2008. In all, 102 patients underwent thyroid surgery, with 90 of these patients also undergoing FNAC. Demographic and thyroid US characteristics of the 102 patients who received thyroid surgery are presented in Table 1. The age of the patients ranged from 13 to 79 years (mean age, 45.5 ± 15.3 years), 86 females and 16 males. Additionally, the statistical power of FNAC in 90 patients was analyzed in Table 2. The statistical analyses of thyroid US in 102 patients including 12 patients not performing FNAC examination was presented in Table 3.

Thyroid US was performed using a real-time ultrasonography scanner with a 10-MHz multi-frequency linear probe (LOGIQ-9; GE Medical Systems, Milwaukee, WI, USA). FNAC was performed by an experienced endocrinologist using a disposable 23-gauge needle except the patients refused. If a cystic lesion was found, the needle size was changed to 18-gauge. If the thyroid showed hypervascularity, the aspiration was performed using a 25-gauge needle. We also used echo aid tapping to draw a cross mark for the thyroid nodules which were categorized as either impalpable, hypervascular, or combined microcalcification. If the nodule

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Benign</th>
<th>Malignant</th>
<th>Total</th>
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<tbody>
<tr>
<td>N</td>
<td>78</td>
<td>24</td>
<td></td>
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<tr>
<td>Mean age (yr)</td>
<td>45.14 ± 15.71</td>
<td>46.88 ± 13.96</td>
<td>NS (0.629)*</td>
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<tr>
<td>Tumor diameter (cm)</td>
<td>2.04 ± 1.94</td>
<td>1.58 ± 1.45</td>
<td>NS (0.295)*</td>
</tr>
<tr>
<td>Female/Male</td>
<td>68/10</td>
<td>18/6</td>
<td>NS (0.198) †</td>
</tr>
<tr>
<td>Echo density</td>
<td>Low/Moderate</td>
<td>36/40</td>
<td>18/5</td>
</tr>
<tr>
<td>Vascularity</td>
<td>Iso/Hyper</td>
<td>33/23</td>
<td>8/9</td>
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* p>0.05, † t-test
‡ p<0.05, # p<0.05, chi-square (x²) test
N: patient number; NS: non-significant

<table>
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<th>Pathology</th>
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<th>Benign</th>
<th>Total</th>
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<tr>
<td>FNAC</td>
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<td>19</td>
</tr>
<tr>
<td>Benign</td>
<td>5</td>
<td>66</td>
<td>71</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>67</td>
<td>90</td>
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Positive predictive value: 94.7% (18/19)
Negative predictive value: 93% (66/71)
Sensitivity: 78.3% (18/23)
Specificity: 98.5% (66/67)
Accuracy: 93.3% (18+66/90)
FNAC: fine needle aspiration cytology

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Malignant</th>
<th>Benign</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>US &amp; FNAC</td>
<td>18</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Benign</td>
<td>6</td>
<td>77</td>
<td>83</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>78</td>
<td>102</td>
</tr>
</tbody>
</table>

Positive predictive value: 94.7% (18/19)
Negative predictive value: 92.8% (77/83)
Sensitivity: 75% (18/24)
Specificity: 98.7% (77/78)
Accuracy: 93.1% (18+77/102)
US: ultrasonography
FNAC: fine needle aspiration cytology
was larger than 3 cm or highly suspected of being a malignancy, aspiration was performed at least twice. The aspirates were placed on the center of glass slides, air dried, and stained using a modified Romanowsky-based Liu method [6].

An adequate smear was considered to contain at least 6 clusters of epithelial cells, with 10 cells or more in each cluster. The FNAC results were categorized into 4 groups: malignant, benign, indeterminate, and unsatisfactory. “Malignant” was defined as typical features of papillary carcinoma, anaplastic carcinoma, medullary carcinoma, or other non-thyroid original carcinomas; “Benign,” as typical, normal follicular cells with pyknotic or colloid content; “indeterminate”, as follicular neoplasm; and “unsatisfactory,” when there were less than 6 cell clusters on a slide, including bloody smears.

Descriptive statistics are expressed as mean ± SD. Student’s t-tests were used to analyze normal distribution data and also compare the means of the continuous variables, age and tumor diameter. Categorical data (gender and echo density) were analyzed using the chi-square ($\chi^2$) test. All statistical tests were two-tailed, and the significance level was set at $p \leq 0.05$.

**RESULTS**

After thyroid surgery, a total of 78 patients were diagnosed as benign (76.5%) and 24 patients as malignant (23.5%), including 20 papillary carcinomas (F/M = 4/1), 1 anaplastic carcinoma (F), 1 medullary carcinoma (F), and 2 metastatic carcinomas (M). The mean diameter of the benign and malignant lesions showed no significantly difference (2.04 ± 1.94 cm vs. 1.58 ± 1.45 cm, respectively; $p = 0.295$). There was also no significant difference for location of the malignant and benign thyroid nodules, grouped either as right, left, or bilateral (9, 7, and 6 cases vs. 25, 19, and 21 cases, respectively; $p = 0.907$). Hypo-echogenicity was significantly more frequent in malignant nodules than in benign nodules (78.3% vs. 47.3%; $p < 0.009$). The use of Hypo-echodensity to predict malignancy had a positive predictive value of 33.3% (18/54 cases), a negative predictive value of 88.9% (40/45 cases), a sensitivity of 21.7% (5/23 cases), and a specificity of 52.6% (40/76 cases). Moreover, 73 patients with thyroid nodules were examined by color Doppler Ultrasound (CDU) before thyroidectomy. The vascular pattern on CDU was classified as either isovascularity or hypervascularity. The histology of isovascularity group included 8 malignant and 33 benign, while in the hypervascularity group, 9 cases were classified as malignant and 23, as benign. These findings indicated that vascularity of thyroid nodules was not a statistically significant predictor of malignancy in our series of cases ($p = 0.388$).

Twelve surgical patients who were investigated by US only before operation, including 4 who refused aspiration examination, 1 who was mentally retarded, and 7 who had a diffuse goiter. One patient was found to have a diffuse goiter containing a tiny calcified spot (Fig. 1) but histology should confirm this to be a papillary microcarcinoma with neck lymph node metastasis.

We reviewed the FNAC results of 90 surgical patients. The cytological diagnoses were grouped into 4 categories: 45 benign (50%), 19 malignant (21.1%), 16 indeterminate (17.8%), and 10 unsatisfactory (11.1%). In the benign group, a total of 21 cases of hemorrhagic or colloid cysts were diagnosed. All these 21 patients had received thyroid surgery, with 1 being postoperatively diagnosed as malignant. The malignancy rate was approximately 4.7% (1/21 cases) in the cystic lesion group. The histopathology reports of the indeterminate group showed 3 cases being diagnosed as malignant (18.7%); 8, as follicular adenoma; and 5, as nodular hyperplasia. The mean age of the indeterminate group was 42.9 ± 20.8 years (range, 13–71 years). There was no difference between the mean age of the 3 malignant patients and the 13 benign patients (42.0 ± 21.4 years and 43.1 ± 21.5 years, respectively; $p = 0.94$, t-test).

![Figure 1. Tiny micro-calcified spot (arrow) in the parenchyma of a diffuse goiter. A papillary microcarcinoma with lymph node metastasis was confirmed by histopathology.](image)
The unsatisfactory group included 10 patients with significant blood smears in the cytology preparations. All these patients received thyroid surgery, with none being postoperatively diagnosed with a malignancy.

Statistical analyses of the predictive potential of FNAC are summarized in Table 2. Of the 19 malignant smears diagnosed by FNAC, 18 were pathologically confirmed as malignant. The positive predictive value for detection of malignancy using FNAC was 94.7% (18/19 cases), and the negative predictive value was 93% (66/71 cases). The cytological diagnosis had a sensitivity of 78.3% (18/23 cases) and a specificity of 98.5% (66/67 cases). As shown in Table 3, the overall positive predictive value for malignancy using combined thyroid US and FNAC was 94.7% (18/19 cases) and the negative predictive value was 92.8% (77/83 cases); the sensitivity was 75% (18/24 cases) and the specificity, 98.7% (77/78 cases).

DISCUSSION

Thyroid nodules are often observed in endocrine clinics. At present, thyroid US and FNAC remain the first-line of treatment and are useful procedures for examining the characteristics of thyroid nodules. Thyroid US with FNAC is also a cost-effective method for preoperatively differentiating between benign and malignant lesions [7-9].

Hypo-echodensity is generally regarded as a marker of suspected malignancy in thyroid nodules. Hypervascularity, especially the type of extensive intranodular pattern on CDU also been used in differentiation of benign and malignant nodules. However, using these single markers to predict malignancy in clinical practice may be associated with poor sensitivity and specificity. Combining thyroid US with FNAC has the potential to improve predictive ability. Whilst diagnostic accuracy may vary between different series of cases, the negative predictive value of FNAC (93%) in our study was comparable to other international reports (60–95%). The positive predictive value for malignancy using FNAC as observed by us (94.7%) was also in accordance with these other studies (70–96%) [10-13].

Possible causes for the one false positive result that we observed included the presence of hypoechoic lesions with positive intranodular vessels as observed by US (Fig. 2a) and uneven chromatin, anisocytosis, and moderate cellularity with inclusion bodies identified in the cytology preparations (Fig. 2b).

Of the 6 false negative cases, the reasons for not diagnosing the malignancy included cystic lesions, aspiration without histologically documented malignant lesions, and indeterminate cases (follicular neoplasm). One patient who did not have a cytological examination was found to have a diffuse goiter with the parenchyma containing only tiny calcified spots. This case proved difficult to diagnose as malignant by US, with subsequent histopathology confirming the presence of a papillary microcarcinoma with lymph node metastasis. Microcalcification and low echodensity were
significantly more frequent in malignant than in benign nodules [14-15, 21]. This indicates that the presence of microcalcification in thyroid nodules increases the possibility of a malignancy and indicates that further workup is necessary.

Figure 3 shows the cytological findings of a false negative case with a nodular goiter and hemorrhagic cyst. A large retrospective review reported 0.65% of cystic changes to thyroid lesions after surgical treatment were diagnosed as thyroid cancer [16]. There is also evidence that the application of echo-guide aspiration cytology may attain more accuracy than freehand FNAC [17]. However, it is also possible that a good aspiration technique and availability of experienced endocrinologists may be more important for achieving high diagnostic accuracy [18, 19].

Another false negative case, despite having high cellularity, was found to have isocytosis on cytological analysis, leading to a diagnosis of nodular goiter (Fig. 4). A diagnosis of multi-focal follicular variant papillary carcinoma was subsequently reported.

The remaining 3 false negative cases were all follicular neoplasms. Although FNAC analysis is
helpful for avoiding unnecessary surgery, indeterminate (follicular neoplasm) smears occur in 10–20% of cases and therefore present a significant diagnostic challenge [20]. Sixteen patients in our study belonged to this category, with 18.7% (3/16 cases) subsequently being diagnosed with a malignancy. Indeterminate FNAC findings were mainly due to an inability to detect the presence of vascular or capsular invasion, which are the diagnostic criteria of follicular carcinoma. Among those indeterminate FNAC smears, atypical cell lesions and age greater than 40 years were shown by Cheung et al. [21] to increase the risk of malignancy. Accordingly, elderly patients should receive thyroid surgery when repeated FNAC reveals atypical cells. In our study, there was no significant difference in age between malignant and benign cases in the indeterminate group. However, a larger series of case studies needs to be investigated, in order to examine, in greater detail, the age-related characteristics of thyroid nodules.

The 10 cases of unsatisfactory sampling in our study represented another limitation of the FNAC examination. Insufficient cellular material was the major reason contributing to the low sensitivity and negative predictive value in this group. The thyroid gland per sé is rich of vessels and therefore CFD US with echo guidance to avoid these vessels should be considered in future clinical applications.

In conclusion, whereas no single US sign independently is fully predictive of malignancy, we suggest that using characteristics of thyroid US combined with FNAC should be a useful strategy for the initial evaluation of thyroid nodules. Up to 18.7% of indeterminate cases were diagnosed as malignant using this approach. Our findings also emphasize that it is important for clinicians to consider the existence of an occult malignancy if cystic changes or microcalcification in a thyroid nodule associated with neck lymph node enlargement are observed.

REFERENCES
8. 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
16. Lin JD, Hsuen C, Chen JY, Liou MJ, Chao TC. Cystic change in thyroid cancer. ANZ J Surg 2007; 77: 450-454
甲狀腺超音波合併細針抽吸細胞學與最終病理診斷在甲狀腺結節的相關性

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林口長庚醫院 內科部 新陳代謝科 4

本研究目的為評估甲狀腺超音波合併細針抽吸細胞學與最終病理結果的相關性。收集 2006 年 1 月至 2008 年 2 月共 1725 位本院病患接受甲狀腺超音波檢查，102 位（5.9%）病患接受手術。在 102 位病患當中，有九十位接受細針抽吸細胞學檢查。細針抽吸細胞學檢查結果分成四類：惡性、良性、不確定與不滿意。將甲狀腺超音波、細針抽吸細胞學與最終病理結果相關性做評估。在 102 位病患中，年齡從 13 歲至 79 歲（平均 45.5 ± 15.3 歲），女性與男性比例為 5.4 比 1。78 位病患診斷為良性（76.5%），24 位病患診斷為惡性（23.5%）（乳突癌 20 例，未分化癌 1 例，髓質癌 1 例與轉移癌 2 例）。90 位接受超音波及細針抽吸細胞學檢查。細針抽吸細胞學檢查偵測惡性的陽性診斷率為 94.7%（18/19 例）、陰性診斷率為 93%（66/71 例）、敏感性為 78.3%（18/23 例）、特異性為 98.5%（66/67 例）。超音波合併細針抽吸細胞學檢查偵測惡性的陽性診斷率為 94.7%（18/19 例）、陰性診斷率為 92.8%（77/83 例）、敏感性為 75%、特異性為 98.7%。16 例細胞學報告為不確定病例當中，有 3 例診斷為惡性（18.7%）。囊性病灶當中有 4.7%（1/21 例）診斷為惡性。1 例乳突性微小癌合併頸部淋巴結轉移顯示只有微小鈣化點存在於甲狀腺實質中。甲狀腺超音波與細針抽吸細胞學檢查在甲狀腺結節初始的評估是有用的。不確定病例應該考慮手術治療。此外我們應注意竄性結節中的微小鈣化合併頸部淋巴結腫大。