Diagnostic accuracy of fine needle aspiration biopsy cytology and ultrasonography in patients with thyroid nodules diagnosed as benign or indeterminate before thyroidectomy

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Abstract. Fine-needle aspiration biopsy cytology (FNABC) and ultrasonography (US) play an important role in differentiating benign thyroid nodules from malignant nodules. We retrospectively investigated the prevalence of follicular thyroid carcinoma (FTC) in patients with thyroid nodules whose FNABC and US readings were not malignant before thyroidectomy. Between 2007 and 2008, 3333 patients underwent thyroidectomy at our institution, and the 737 of them who had thyroid nodule that had been diagnosed as hyperplastic nodule or follicular tumor by FNABC and US preoperatively were the subjects in this study. Postoperative histopathology showed hyperplastic nodule in 416 patients, follicular adenoma in 200 patients, FTC in 99 patients, and other disease in 22 patients. By FNABC, 34 (6.7%) of the 505 patients with diagnosis as benign and 65 (28%) of the 232 patients with diagnosis as indeterminate, were diagnosed as having FTC. The diagnosis was FTC in 56 (9.6%) of the 582 patients with a preoperative diagnosis of hyperplastic nodule by US and 43 (27.7%) of the 155 patients with a diagnosis of follicular tumor by US. The diagnosis of FTC was made in 21 (4.8%) of 438 patients who were concurrently diagnosed as benign by FNABC and as hyperplastic nodule by US, and in 30 (34.1%) of 88 patients who were diagnosed as indeterminate by FNABC and follicular tumor by US. FNABC has been the mainstay for the preoperative evaluation of thyroid nodule. The results of this study showed that US can also be a useful tool for diagnosing FTC.

Key words: Follicular thyroid carcinoma, Fine needle aspiration biopsy cytology, Ultrasonography, Preoperative diagnosis

THYROID NODULES are frequently encountered in outpatient setting [1-3]. Most thyroid nodules are evaluated by several modalities in order to determine whether surgical indications are present. Fine needle aspiration biopsy cytology (FNABC) is the most important diagnostic modality in the initial workup of patients with thyroid nodule. Most pathologists group specimens obtained by FNABC into one of several diagnostic categories: malignant, suspicious, indeterminate (including atypia of undetermined significance and atypical cellular lesion), benign, or inadequate. The discrimination between malignant and benign lesions by cytology is considered excellent for purposes of preoperative evaluation [4-8], but there are significant limitations in those readings that provide clinically useful information. One of these is the indeterminate cytology reading. The risk of malignancy in patients whose FNABC specimens are indeterminate is reported to be anywhere from 14-42% [9-15]. Follicular thyroid adenoma (FTA) and follicular thyroid cancer (FTC) can give indeterminate readings on FNABC. Recently, some studies have shown that molecular analysis of thyroid nodules can be applied in a clinical setting and can improve the accuracy of the diagnosis [16-23]. However, none of the methods has been fully validated to the extent that it is in general use in the routine diagnostic laboratory. On the other hand, advance in the resolving power of ultrasonography (US) apparatus have provided more information not only concerning the location of thyroid nodules, but also features that are associated with benign nodules and features associated with malignant nodules [24-29]. Papillary thyroid carcinoma (PTC) can now be identified with reasonably high accuracy not only by
Between January 2007 and December 2008, 3333 patients underwent thyroidectomy at our institution. The 737 patients who did not have a diagnosis of malignancy by FNABC and US before thyroidectomy were the subjects of this study. None of these patients had previous thyroid surgery or had a history of neck irradiation. There were 585 females and 152 males. Their median age was 51 years (range: 12 to 82 years old). The final diagnosis was made by postoperative histopathological examination of the surgical specimens, and concomitant incidental micropapillary carcinomas were excluded from the final diagnosis.

Total thyroidectomy was performed for patients with multinodular goiter diagnosed as hyperplastic nodule preoperatively. Hemithyroidectomy was performed if the nodule was classified as indeterminate by FNABC, and completion total thyroidectomy was performed if postoperative histology showed malignancy. The study was reviewed and approved by the Institution’s Ethics Board and performed in accordance with the Declaration of Helsinki.

Subjects and Methods

Patients

At our institution, patients with thyroid nodules routinely have US of the nodules and thyroid function and related tests including serum triglyceride (Tg), anti-Tg antibodies (TgAb), and anti-thyroid peroxidase antibodies (TPOAb), all US at their first visit. When nodules are not entirely cystic according to the US images, FNABC is performed under US guidance. Preoperative tests that we consider indicative of malignancy are cytology readings, “malignant” or “suspicious for malignancy”, or US readings, “cancer.” The indications for thyroid surgery at our institution for patients in whom these tests are not indicative of malignancy are a goiter of approximately more than 5 cm in diameter, goiter that extends into the mediastinum, symptoms due to compression by a goiter, and indeterminate cytology and/or a diagnosis of a follicular tumor based on the US findings (Table 1). We treat patients with a preoperative diagnosis of follicular tumor or FTA surgically because FTC is difficult to distinguish from FTA preoperatively, and because minimally invasive FTC does not always have favorable prognosis [34]. Patients who did not have thyroid surgery were followed in our outpatient clinic at 6 to 12 month intervals. US was routinely performed at every follow-up visit and FNABC was performed when a follicular tumor or cancer was suspected on the basis of the US findings or when the nodule increased in size.

Ultrasonographic evaluation

The ultrasound scanners used were HDI 5000 7-15-MHz linear probe (Philips Medical Systems, Bothell, Wash. USA), LOGIQ 9 7-15-MHz linear probe (GE Medical Systems, Milwaukee, WI USA), Voulson 730 (GE Medical Systems), and Voulson E8 (GE Medical Systems). US examination was made by sonographers who had trained for at least 6 months in the ultrasonography center of our institution, and the evaluation and diagnosis were made by the attending endocrinologists and endocrine surgeons according to the ultrasound findings and the diagnostic criteria that are used in our institution (Table 1). The US features of the thyroid nodules were evaluated according to size, shape, margin, echogenicity, calcification, and internal color flow. Internal echo flow was defined as centripetal flow seen within the nodule. The US diagnoses of thyroid nodules were classified into 3 categories, hyperplastic nodule (HN), follicular tumor (FT), and Cancer. In the US diagnosis categories, HN means adenomatous nodule (goiter), FT means follicular adenoma or follicular carcinoma, and Cancer means papillary carcinoma or anaplastic carcinoma. All the patients in this study had been diagnosed with HN or FT based on the US findings.

Fine needle aspiration biopsy cytology

Endocrinologists and endocrine surgeons who had its features on cytology, but also by its US features. In contrast, at least as far as FTC is concerned, it is difficult to differentiate FTC from FTA by these modalities. Several papers have reported characteristic sonographic features of FTC [30-33]. However, US is currently not considered an accepted method for the diagnosis of FTC and its role to allow clinicians to assess the likelihood that a thyroid nodule is FTC, as compared to FTA, is uncertain. Distant metastases are more common in FTC than in PTC and the prognosis is poorer. Preoperative tests to assess the likelihood of FTC in thyroid nodules, and thus reduce surgical procedures that are likely to be unnecessary, are very much needed.

The purpose of this study is to know how accurately US and FNABC can diagnose FTC before thyroidectomy and we retrospectively studied patients with thyroid nodules that had been characterized by US and FNABC as “apparently not malignant” before thyroidectomy.
Diagnostic accuracy in thyroid nodule

Histological diagnosis and patients’ characteristics

The postoperative histopathological diagnosis was HN in 416 patients, FTA in 200 patients, FTC in 99 patients (minimally invasive FTC in 82, widely invasive FTC in 17), and other thyroid disease in 22 patients, including PTC in 13 (ordinary in 8, follicular variant in 4, macrofollicular variant in 1), medullary thyroid carcinoma in 2, hyalinizing trabecular tumor in 3, Hashimoto thyroiditis in 2, and metastatic malignant tumor from another organ in 2 (one from renal cell carcinoma, and the other from a sarcoma of unknown origin). There were 116 patients (15.7%) who had a malignant thyroid nodules and the proportion of these patients who had FTC and PTC was 85.3% and 11.2%, respectively.

Preoperative US diagnosis and histopathological findings

The US diagnosis was HN in 582 patients (79%) and FT in 155 (21%) patients. The final histopathological diagnosis was malignant disease in 67 (11.5%) of the 582 patients with preoperative diagnosis of HN.
Table 2  Histopathological diagnosis and patients' characteristics

<table>
<thead>
<tr>
<th>Histopathological diagnosis n (%)</th>
<th>HN</th>
<th>FTA</th>
<th>FTC</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>340 (81.7)</td>
<td>154 (77)</td>
<td>62 (75.6)</td>
<td>13 (76.5)</td>
</tr>
<tr>
<td>Male</td>
<td>76 (18.3)</td>
<td>46 (23)</td>
<td>20 (24.4)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40 y</td>
<td>116 (27.9)</td>
<td>70 (35)</td>
<td>25 (30.5)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>&gt;40 y</td>
<td>300 (72.1)</td>
<td>130 (65)</td>
<td>57 (69.5)</td>
<td>12 (70.6)</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40 mm</td>
<td>113 (27.2) a,b</td>
<td>80 (40) a,c</td>
<td>39 (47.6) b,c</td>
<td>10 (58.8) b,c</td>
</tr>
<tr>
<td>&gt;40 mm</td>
<td>303 (72.8)</td>
<td>120 (60)</td>
<td>43 (52.4)</td>
<td>7 (41.2)</td>
</tr>
<tr>
<td>Thyroglobulin*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤500 ng/mL</td>
<td>251 (68) d,e</td>
<td>97 (54.8) d</td>
<td>31 (41.3) e</td>
<td>8 (47.1) e</td>
</tr>
<tr>
<td>&gt;50 ng/mL</td>
<td>118 (32)</td>
<td>80 (45.2)</td>
<td>44 (58.7)</td>
<td>9 (52.9)</td>
</tr>
</tbody>
</table>

HN, hyperplastic nodule; FTA, follicular adenoma; FTC, follicular thyroid carcinoma

a, HN vs. FTA p<0.002; b, HN vs. FTC p<0.001; c, FTA vs. FTC p<0.05; d, HN vs. FTA p<0.001; e, HN vs. FTC p<0.001; *, patients with positive TgAb were excluded

Table 3  US diagnosis and histopathological diagnosis

<table>
<thead>
<tr>
<th>US Diagnosis</th>
<th>Histopathological diagnosis n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HN</td>
<td>FTA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HN</td>
<td>380 (65.4)</td>
<td>130 (22.3)</td>
</tr>
<tr>
<td>FT</td>
<td>36 (23.2)</td>
<td>70 (45.1)</td>
</tr>
<tr>
<td></td>
<td>416</td>
<td>200</td>
</tr>
</tbody>
</table>

HN, hyperplastic nodule; FT, follicular tumor; FTA, follicular adenoma; FTC, follicular thyroid carcinoma

by US, and of these patients there were 56 (9.6%) with FTC. Of the 155 patients with a diagnosis of FT by US the final diagnosis was malignant in 49 (31.6%), 43 (27.7%) of whom had FTC (Table 3). Patients with widely invasive FTC were observed in 7 (1.2%) of patients with US diagnosis of HN, and 10 (6.5%) of patients with US diagnosis of FT.

The histopathological diagnoses for US findings of multinodularity and cystic change are presented in Table 4. Both multinodularity (HN vs. FTA p=0.001, HN vs. FTC p=0.005) and cystic change (HN vs. FTA p<0.0001, HN vs. FTC p<0.0001) were significantly more frequent in the patients with hyperplastic nodule than in the patients with FTA and FTC. However, the frequency of multinodularity and cystic change were similar in patients with FTC and FTA.

**FNABC diagnosis and histopathological findings**

The accuracy of the preoperative FNABC diagnoses based on the histopathological diagnosis is presented in Table 5. Of the 505 patients with a preoperative diagnosis of “benign” by FNABC, the nodule was malignant in 42 patients (8.3%), 34 of whom had FTC (6.7%). Of the 232 patients with a preoperative diagnosis of “indeterminate” by FNABC, the nodule was malignant in 74 (31.9%), 65 (28%) of whom had FTC.

Patients with widely invasive FTC were observed in 5 (1%) of patients with FNABC diagnosis of benign, and 12 (5.2%) of patients with FNABC diagnosis of indeterminate.

**Combination of US and FNABC diagnosis and histopathological findings**

The rates of thyroid malignancy and FTC in patients with 4 categories based on US and FNABC readings are shown in Table 6. Malignant tumor were diagnosed in 5.7 % of the patients who had HN in US reading and benign in FNABC reading and in 36.4% of the patients who had FT in US readings and indeterminate in...
FNABC reading. FTC was diagnosed in 34.1% of the patients who had FT in US readings and indeterminate in FNABC reading, 4.8% of the patients who had HN in US reading and benign in FNABC reading, and in approximately 20% of patients with either FT in US reading and indeterminate in FNABC reading. When the nodule was examined only by FNABC, FTC was diagnosed in 34 of 505 patients with benign in FNABC reading (6.7%). On the other hand, when combined FNABC with US, FTC was diagnosed in 13 of 67 patients with benign in FNABC reading and FT in US reading (19.4%).

**Discussion**

FNABC has been main diagnostic tool because it is safe, accurate, and simple. The use of FNABC has resulted in a decrease in the number of benign nod-
As a result of improvements in technology US is now being used to characterize distinct features in the images of thyroid nodules. The US features of thyroid nodules have been studied, and predictive malignant features were reported [24-29]. The US features of follicular tumor, including follicular carcinomas and follicular adenomas, have been reported to be: isoechoic/hypoechoic echotexture, predominantly solid and homogenous, well defined halo, and central internal color flow [30-33]. However, we think that the role of US in diagnosing follicular tumors lies in differentiating follicular tumors from hyperplastic nodules, not in differentiating follicular carcinomas from adenomas.

A comprehensive diagnostic strategy appears be necessary to manage follicular tumor and, we demonstrated that US and FNABC played complementary role in diagnosing follicular carcinoma. Of 438 patients who were concurrently diagnosed as having a benign nodule by FNABC and having HN by US, 21 (4.8%) were diagnosed with FTC after thyroidectomy, and only 1 (0.2%) of them was diagnosed with widely invasive FTC. The result of this study demonstrated that follicular carcinoma can be rather correctly diagnosed by both modalities. The adequacy of our surgical indication is supported by the fact that the patients with follicular carcinoma, especially the patients with widely invasive follicular carcinoma, underwent surgery within a significantly shorter interval after the diagnosis was made than the patients with hyperplastic nodule. However, this study has potential limitation because it was retrospective study and there was inevitable bias in patient selection. Not all patients with thyroid nodules have indications for surgery and most of patients with thyroid nodules are followed up without surgical treatment.

**Declaration of Interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References


