Biological Behavior of Papillary Thyroid Carcinomas that Mimic Benign Nodules or Follicular Tumors on Imaging Studies

Yasuhiro Ito1*, Mitsuyoshi Hirokawa2, Kaoru Kobayashi1, Minoru Kihara1, Akira Miyauchi1

1Department of Surgery and 2Department of Pathology, Kuma Hospital, Kobe, Japan.

Abstract

Papillary thyroid carcinoma (PTC) shows typical ultrasonographic features such as a solid, irregular border, presence of psammoma calcification, and extrathyroidal invasion. However, it sometimes mimics a benign nodule or follicular tumor on ultrasound. In this study, we investigated the biological behaviors of 542 PTC that were not diagnosed as PTC on ultrasound. All but 6 underwent fine needle aspiration biopsy and 494 were cytologically diagnosed as or suspected of PTC. Of the 542 PTC, 198 were follicular variant (FVPC, n = 79), macrofollicular variant (n = 22), encapsulated PTC (n = 85), and cribriform morular variant (CMV, n = 12); these were classified into Group A. The remaining 344 were PTC with papillary growth pattern without encapsulation at histological examination, and were classified into Group B. Group A was less likely to show pathologically node metastasis and extrathyroid extension than Group B, but prognosis did not differ between the groups (5-year disease-free survival rate, 99%). Since pathologically node metastasis was rather frequent (21% in Group A and 36% in Group B), thyroidectomy with at least central node dissection was necessary for these patients; prognosis, however, was almost equal in both groups.

Keywords: Papillary thyroid carcinoma, ultrasonography, lymph node metastasis, prognosis

Introduction

Papillary thyroid carcinoma (PTC) is the most common malignancy arising from thyroid follicular cells. Generally, it exhibits an excellent prognosis, although certain clinicopathological characteristics predict a dire prognosis. PTC is rather easily diagnosed based on typical ultrasonographic characteristics such as irregular shape, fine strong echoes, and fine needle aspiration biopsy (FNAB). However, some PTCs have been treated without a diagnosis of PTC even on cytology, with patients undergoing surgery such as enucleation or thyroidectomy without lymph node dissection for benign diseases. Previous studies have demonstrated that such PTCs have an indolent character and immediate reoperation is not necessary (1, 2).

On the other hand, Fukushima et al. have shown that medullary thyroid carcinoma (MTC) mimicking follicular tumor or benign nodule on ultrasonography is highly indolent because of the low incidence of lymph node metastasis and no extrathyroid extension nor tumor recurrence, even though most of them were preoperatively diagnosed as MTC on cytology with high CEA and/or calcitonin levels (3). These results prompted us to examine the biological behavior of benign-looking PTC on ultrasonography. In this study, we investigated the biological characteristics of PTC mimicking the follicular tumor or benign nodule on sonographic findings.

Patients and Methods

We enrolled 542 patients (107 males and 435 females, median age at surgery 54 years) with PTC larger than 1 cm in diameter that were ultrasonographically diagnosed as benign nodule (US class II) or follicular tumor (US class III) subject to our criteria published by Yokozawa et al. being US class II as round and cystic nodule (single or multiple) or isoechoic solid nodule; and US class III as round and hypoechoic solid nodule (4). All patients underwent thyroidectomy (total thyroidectomy in 310, and hemithyroidectomy in the remaining 232) with or without lymph node dissection (no dissection in 25, central dissection only in 413, and central and uni- or bilateral modified radical neck dissection in 104 patients) between 2005 and 2010. The tumor size ranged from 11 to 120 mm (median 23 mm) in diameter. Patients having other thyroid malignancies such as follicular, medullary, and anaplastic carcinoma, and those with coexisting other PTCs strongly suspected by ultrasonography, were deleted from our series. Papillary microcarcinoma measuring 1 cm or less in diameter was also excluded. All patients were pathologically diagnosed as PTC with or without lymph node metastasis.

Of the 542 PTC, 198 were follicular variant (FVPC, n = 79), macrofollicular variant (n = 22), encapsulated PTC (n = 85) and cribriform morular variant (CMV, n = 12); these were classified into Group A. The remaining 344 were PTC with papillary growth pattern without encapsulation at histological examination, and were classified into Group B. The diagnosis of “encapsulated PTC” was based on the representative hematoxylin and eosin (H-E) sections, because we did not produce H-E sections from whole tumor. After surgery, we followed patients once or twice per year to check for PTC recurrence by blood examination, ultrasonography, and chest roentgenography or CT scan. The median follow-up time was 70 months (6-117 months). We regarded patients as having recurrence only when recalled lesions were detected on imaging studies. Suspicious lymph node lesions underwent FNAB and thyroglobulin level of the washout fluid of needle was used for FNAB, measured as described by Uruno et al. for diagnosis of metastasis (5).
A Fisher’s exact test was employed for comparing the values. A Kaplan-Meier method and log-rank test were adopted for analyzing disease-free survival (DFS) rates of patients. A P-value less than 0.05 was considered significant.

Results

Of the 542 PTCs, 536 underwent FNAB before surgery. Four hundred and ninety-four (92%) were cytologically diagnosed as or suspected of PTC, and the remaining 43 (8%) were diagnosed as benign nodule or follicular tumor. None of the patients showed distant metastases at surgery. The incidence of clinicopathological findings showing an aggressive behavior was low in our series. Only 17 (3%) had clinical node metastases on preoperative imaging studies. Minimal and significant extrathyroid extension was detected in only 19 (4%) and 4 (1%), respectively, on intraoperative findings. Of the 510 patients who underwent at least central neck dissection, 166 (33%) were diagnosed as pathologically node-positive.

Table 1: Relationship between histology and clinicopathological features for 542 PTCs diagnosed as benign nodule or follicular tumor on ultrasound

<table>
<thead>
<tr>
<th>N factor</th>
<th>*Group A (n = 198)</th>
<th>**Group B (n = 344)</th>
<th>Total (n = 542)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>191 (96%)</td>
<td>334 (97%)</td>
<td>525 (97%)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>7 (4%)</td>
<td>10 (3%)</td>
<td>17 (3%)</td>
<td>0.69</td>
</tr>
<tr>
<td>pN factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>145 (79%)</td>
<td>206 (64%)</td>
<td>351 (68%)</td>
<td></td>
</tr>
<tr>
<td>pN1</td>
<td>39 (21%)</td>
<td>127 (36%)</td>
<td>166 (32%)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Unknown</td>
<td>14</td>
<td>11</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

***Extrathyroid extension

<table>
<thead>
<tr>
<th>Extension</th>
<th>*Group A (n = 198)</th>
<th>**Group B (n = 344)</th>
<th>Total (n = 542)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>195 (98%)</td>
<td>324 (94%)</td>
<td>519 (96%)</td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>2 (1%)</td>
<td>17 (5%)</td>
<td>19 (3%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Significant</td>
<td>1 (1%)</td>
<td>3 (1%)</td>
<td>4 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

FNAB findings

<table>
<thead>
<tr>
<th>Tumor</th>
<th>*Group A (n = 198)</th>
<th>**Group B (n = 344)</th>
<th>Total (n = 542)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVPC</td>
<td>176 (90%)</td>
<td>317 (93%)</td>
<td>493 (92%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Macrofollicular variant</td>
<td>19 (10%)</td>
<td>24 (7%)</td>
<td>43 (8%)</td>
<td></td>
</tr>
<tr>
<td>Encapsulated PTC</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>0</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

To date, 8 patients (1%) have had a recurrence (lung and lymph node in 2, lymph node in 5, and subcutaneous tissue in 1 patient). We investigated the DFS of these patients by Kaplan-Meier method and their 5-year DFS rate was 99%. Of the 8 patients who experienced recurrence, 7 were diagnosed as PTC on preoperative cytology, and only 1 (FVPC) belonged to Group A. However, neither cytological results nor Group classification was proven significant (P = 0.1568 and P = 0.6302 by log rank test, respectively). To date, none of the patients in our series has died of PTC.

Discussion

Ultrasound is useful for evaluating thyroid tumors whether they are malignant or benign, although it is difficult to discriminate follicular carcinoma from adenoma. PTC is the most common thyroid carcinoma and is rather easy to be diagnosed based on ultrasonographic findings. However, PTC occasionally mimics benign nodules or follicular tumors on ultrasonographic findings without any imaging evidence of PTC, which is difficult to be diagnosed on ultrasonography.

In this study, however, we demonstrated that 92% of these could be diagnosed as PTC on cytology, which was not discrepant with our previous report (6), suggesting that FNAB can diagnose most PTC even though they resemble benign nodule or follicular tumor. Another important point is that such PTC tumors have very low incidence of high-risk features such as clinically apparent node metastasis and significant extrathyroid extension (7), which should indicate an excellent prognosis (5-year DFS rate, 99%).
In our series, 63% were PTC with papillary growth but without encapsulation, while the remaining 37% were FVPC (15%), macrofollicular variant (4%), encapsulated PTC (16%) and CMV (2%). The incidence of PTC with papillary growth pattern was smaller than in our previous study that we enrolled PTC patients regardless of ultrasonographic findings, indicating that the incidence of FVPC, macrofollicular variant, encapsulated PTC and CMV increased in the series of tumors mimicking benign disease or follicular tumor.

We have previously demonstrated that FVPC has a prognosis similar to the conventional PTC throughout our series (8). In this series, however, only 1 in 75 patients showed a recurrence, which was better than in our previous study. This was probably because of selection bias that we extracted benign-looking FVPC on ultrasonographic findings. Liu et al. assumed that FVPC should be separated into encapsulated and nonencapsulated (infiltrative/diffuse) types and the former can be further subdivided into tumors with or without capsular/vascular invasion (9). In their series, none of noninvasive, encapsulated FVPC showed lymph node metastasis or extrathyroid extension. In our series, 11 patients were diagnosed noninvasive, encapsulated FVPC, although one patient had lymph node metastasis in the central compartment. The discrepancy is probably because we diagnosed encapsulated PTC based on the representative H-E sections, but not on the sections from whole tumors, as described in the Patients and Methods section. Yang et al. demonstrated the diagnostic difficulty of encapsulated FVTC (10). In our series, 9 of 11 patients (90%) were cytologically diagnosed or suspected of PTC, but the remaining 2 were not. These 2 cases underwent thyroidectomy only. However, none of these cases showed carcinoma recurrence to date, indicating that encapsulated FVTC has a very indolent character and shows an excellent prognosis. Vivero et al. have also recently demonstrated that fully or partially encapsulated FVTC has less metastatic potential and recurrence risk than infiltrative FVPC, which is coincident with our findings (11).

Macrofollicular variant was initially reported by Albores-Saavedra et al. (12). Although pathological node metastasis was often found in our previous study (13), it has shown an excellent prognosis for long-term follow-up. Also in this series, no patients showed a recurrence. Lack of extrathyroid extension and clinical node metastasis should be the reasons for an excellent prognosis.

Our series included 85 encapsulated PTC, but the incidence of pathological lymph node metastasis was rather high at 21%, although lower than that of non-encapsulated PTC with papillary growth. Theoretically, if completely encapsulated, lymph node metastasis would not occur. However, we did not examine entire cut surfaces of tumor, only the maximum cut surface of each. It is therefore suggested that lymph node metastasis could have occurred due to the tumor encapsulation having been broken. However, in our previous study, only 7% of patients showed recurrence and disease-free survival was better than conventional PTC (14). Moreover in this series, none of the patients showed a recurrence.

CMV is known to be related to familial adenomatous polyposis (FAP) associated with the APC gene mutations, and can occur sporadically in relation to colonic polyposis (15). Both are likely to be detected in young females. It is generally indolent and extrathyroid extension and lymph node metastasis are extremely rare (15,16). Although most of the CMV can be cytologically diagnosed, it is difficult to diagnose PTC based on imaging studies. This finding was not discrepant with that by Chong et al. (17).

Our series included 63% PTC with papillary growth. Although the incidence of pathological lymph node metastasis was higher than that in Group A, the incidences of high-risk features such as clinical node metastasis and significant extrathyroid extension were still lower compared with our previous studies (18). This suggests PTC without encapsulation also has an indolent character and shows an excellent prognosis if its ultrasonographic profile mimics follicular tumor or benign nodule.

In summary, PTC with ultrasonographic findings mimicking follicular tumor or benign nodule is slow-growing and unlikely to show a recurrence after surgery, regardless of its histological type. Thyroidectomy with at least central node dissection is necessary for patients with PTC that mimics benign nodules or follicular tumors on ultrasonographic findings because of high incidence of pathological node metastasis; patient prognoses, however, are excellent.

**Conflicts of Interest:** None

**References**


10. Yang GC, Fried K, Yokoshina TV, Schreiner AM. Encapsulated follicular variant of papillary thyroid carcinoma:


