An Observation Trial Without Surgical Treatment in Patients with Papillary Microcarcinoma of the Thyroid

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The recent prevalence of ultrasound-guided fine-needle aspiration biopsy has resulted in a marked increase in the number of patients with papillary microcarcinoma (maximum diameter, \( \leq 10 \text{ mm} \)) of the thyroid detected by this sophisticated tool. On the other hand, it is debatable whether patients with papillary microcarcinoma should always undergo surgery after diagnosis, because a high incidence of occult papillary carcinoma has been observed in autopsy studies. Thus, we proposed observation without surgical therapy as a treatment option in 732 patients diagnosed with papillary microcarcinoma by the above technique from 1993 to 2001. One hundred sixty-two patients chose observation and were classified as the observation group. During the follow-up period for patients in the observation group, more than 70% of tumors either did not change or decreased in size compared to their initial size at diagnosis. They enlarged by more than 10 mm in 10.2%, and lymph node metastasis in the lateral compartments appeared in only 1.2% of patients during follow-up. On the other hand, 570 patients chose surgical treatment at diagnosis and 56 patients in the observation group who underwent surgery after a period of follow-up were classified as the surgical treatment group. Of these 626 patients, lymph node dissection was performed in 594 patients, and metastasis was confirmed histologically in 50.5%. Multiple tumor formation was seen in 42.8% of patients. In this group, the rate of recurrence was 2.7% at 5 years and 5.0% at 8 years after surgery. Our preliminary data suggest that papillary microcarcinomas do not frequently become clinically apparent, and that patients can choose observation while their tumors are not progressing, although they are pathologically multifocal and involve lymph nodes in high incidence.

Introduction

THYROID CARCINOMA is the most common malignancy originating from the endocrine organs. Papillary carcinoma is the representative type and is generally mild and grows slowly. The recent prevalence of ultrasonography in thyroid or carotid artery lesion screening has led to the detection of numerous small thyroid lesions. Fine-needle aspiration biopsy (FNAB) can diagnose papillary carcinoma in lesions larger than 3 mm (1). Thyroid carcinomas of 10 mm or less in maximum diameter are defined as microcarcinoma according to the World Health Organization classification. Previous studies have shown that papillary microcarcinoma accounted for up to 30% of all papillary carcinoma (2), with an excellent prognosis after surgical treatment (3–7). On the other hand, papillary microcarcinoma is known to have a high incidence of lymph node metastasis and multiple tumor formation; lymph node metastasis was pathologically detected in 16%–64% and multiple tumor formation was in 23%–33% in studies in the United States, Spain, and Japan (3–7), which may be a reason for recommending thyroidectomy with lymph node dissection. However, it remains debatable whether all papillary microcarcinomas grow and become clinically apparent and life-threatening for patients during their lifetime.

If the answer is no, it may not be appropriate for surgeons to recommend surgical treatment for all patients diagnosed with microcarcinoma. In this study, we investigated the impact of changes in size and other characteristics, such as lymph node metastasis and multiple tumor formation under observation with periodic follow-up, in order to clarify how this disease should be treated.

Patients and Methods

Patients

From 1993 to 2001, 2869 patients underwent surgery under the FNAB diagnosis of papillary carcinoma of the thyroid in Kuma Hospital. The FNAB methods in our hospital
have been previously described (1). The diagnosis of papillary carcinoma was made based on the features typical for this disease such as nuclear grooves, intranuclear and cytoplasmic inclusions, and dust nuclear chromatin (8) by two specialists (A.M. and S.K.). Among the patients, 2838 were confirmed to have papillary carcinoma by postoperative pathologic examination, indicating that the positive predictive value (PPV) of FNAB for papillary carcinoma in our hospital is 98.9%.

In the same period, 732 patients were diagnosed as having papillary microcarcinoma by FNAB. The majority of these patients had been identified as having suspicious thyroid lesions at other clinics using ultrasonography and had been referred to our hospital. We provided two therapy options—immediate surgical treatment or observation without surgery—for all patients except for those with unfavorable features such as tumors located adjacent to the trachea, tumors possibly invading the recurrent laryngeal nerve, FNAB findings suggesting high-grade malignancy, and/or lymph nodes highly suspicious of metastasis (or confirmed as metastasis by FNAB) in the lateral compartment detected by ultrasonography. We recommended surgical treatment for patients with these unfavorable features. We regard lymph nodes as suspicious of metastasis when they are high echoic and/or round in shape with high length to depth ratio. We only occasionally perform FNAB in lymph nodes in the central compartment, but we often do so for lymph nodes suspicious of metastasis in the lateral compartment in order to confirm the indication and design of surgery. This project was approved by the Ethics Committees in our hospital and informed consent was obtained from all participating patients. As a result, 162 patients chose observation without surgical treatment, and the remaining 571 patients underwent surgical treatment after diagnosis.

The background of the 162 patients in the observation group at the initiation of follow-up is summarized in Table 1. Their follow-up was performed by ultrasonography investigating the diameter of the carcinoma as well as the appearance of multiple tumor foci and lymph node metastases once or twice per year. The follow-up time ranged from 18 to 113 months and averaged 46.5 ± 21.5 months (mean ± standard deviation [SD]). Levothyroxine was administered to 11 patients to suppress the thyroid-stimulating hormone (TSH) as the patients’ choice. For statistical analyses of the changes in size of the carcinoma for patients in the observation group, we plotted the size of the carcinoma in each patient every year after diagnosis.

The patients belonging to the surgical treatment group consisted of 571 patients who underwent surgery at the diagnosis, and 56 patients from the observation group who underwent surgery after a certain period of follow-up. Of these 627 patients, 1 was treated by another hospital because of liver dysfunction and was omitted from our statistical analysis. The 626 patients accounted for 21.8% of those who underwent surgery under the diagnosis of papillary carcinoma from 1993 to 2001 in our hospital. All had been histologically diagnosed with papillary carcinoma by pathologic examination, with the result that the PPV of FNAB of papillary microcarcinoma in this series was 100%. The background of these 626 patients at the time of operation is summarized in Table 1. Those patients who underwent surgical treatment were followed up once to a few times per year by ultrasonography with or without chest roentgenography.

### Statistical analyses

We adopted the paired *t* test to compare the average tumor size in each follow-up period and at the beginning of follow-up. Furthermore, the Kaplan-Meier method was adopted to evaluate the disease-free survival (DFS) of patients who underwent surgery. A *p* value less than 0.05 was regarded as statistically significant.

### Results

#### Observation group

**Tumor size.** We classified the patients in each ultrasound examination into one of three categories: increased, de-

<table>
<thead>
<tr>
<th>Variables</th>
<th>Observation group</th>
<th>Surgical treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
<td><strong>Observation group</strong></td>
<td><strong>Surgical treatment group</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>52.3 ± 12.3 years (23–80 years)</td>
<td>51.9 ± 11.4 years (16–83 years)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (3.1%)</td>
<td>39 (6.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>157 (96.9%)</td>
<td>587 (93.8%)</td>
</tr>
<tr>
<td><strong>Tumor size</strong></td>
<td>6.9 ± 3.0 mm (3–10 mm)</td>
<td>7.5 ± 1.9 mm (3–13 mm)</td>
</tr>
<tr>
<td><strong>Suspicion of multiple carcinoma foci</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (18.5%)</td>
<td>196 (31.3%)</td>
</tr>
<tr>
<td>No</td>
<td>132 (81.5%)</td>
<td>430 (68.7%)</td>
</tr>
<tr>
<td><strong>Suspicion of lymph node metastases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (6.8%)</td>
<td>121 (19.3%)</td>
</tr>
<tr>
<td>No</td>
<td>151 (93.2%)</td>
<td>505 (80.7%)</td>
</tr>
<tr>
<td><strong>Associated thyroid tumors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>107 (66.0%)</td>
<td>350 (55.9%)</td>
</tr>
<tr>
<td>No</td>
<td>55 (34.0%)</td>
<td>276 (44.1%)</td>
</tr>
</tbody>
</table>

*a* Surgical treatment group includes 56 patients who underwent surgery after follow-up, who are also included in the observation group.
increased, and unchanged size. We regarded the tumor size of each patient as having increased or decreased when their maximum diameters increased or decreased by 2 mm or more as compared to those at the beginning of follow-up, otherwise, we classified them as unchanged. Table 2 indicates the change in size of the microcarcinoma of patients in the observation group. By paired t test, the average tumor sizes after follow-up of 3 years and 4 years were significantly larger than at the beginning. However, the tumor size of more than 70% of patients did not increase at any of the follow-up examinations, and 72.3% did not increase in size, even after 5 years or more. We could find no difference of carcinoma size change between patients with and without levothyroxine medication (data not shown).

During the follow-up, the size of the tumor exceeded 10 mm in 18 patients (11.1%). We continued to follow 11 of them, and no patients showed a further increase in size at their next examination. The remaining 7 patients underwent surgical treatment because of patient choice or the surgeon’s preference. Unexpectedly, the carcinoma lesion of 5 patients became undetectable by ultrasonography during follow-up. Three were detected again in the next examination, but two remained undetectable in the most recent examination.

Other characteristics. The criteria of lymph nodes suspicious of metastasis by ultrasound are described in Materials and Methods. Under these criteria, lymph node metastasis was suspected by ultrasonography in 20 (12.3%) of the 162 patients in the observation group. In 11 patients, it was detected at the beginning of follow-up (Table 1) and appeared during follow-up in the remaining 9 patients. Eighteen patients were suspected of having lymph node metastasis in only the central compartment but surgery was not performed. The number and size of the nodes had not increased in the subsequent examination. In the remaining 2 patients (1.2%), lymph nodes suspicious of metastasis appeared in the lateral compartment during follow-up by ultrasound. One case was confirmed by FNAB, and surgery was performed. Although FNAB was negative in another case, we recommended surgery because of the appearance of multiple lymph nodes that were highly suspicious of metastasis.

Multiple tumor formation was suspected in 48 patients (29.6%), and was detected at the beginning of follow-up in 30 patients (18.5%) (Table 1). It was confirmed by FNAB in 3 patients at the beginning of follow-up and 5 patients during follow-up. The association of other benign nodules such as adenomatous nodules, follicular tumor and adenomatous goiter was observed in 107 patients (66.0%) (Table 1).

Summary of patients who underwent surgical treatment after observation. Of the 162 patients in the observation group, 56 underwent surgical treatment after a certain period of follow-up ranging from 19 to 56 months. The tumor size in these 56 patients had increased in 13 patients (23.2%), decreased in 7 (12.5%), and was unchanged in the remaining 36 (64.3%). Seven (12.5%) exceeded 10 mm during follow-up, and the surgery was recommended. Two decreased to less than 10 mm before surgery, and the remaining 5 were classified as T2 (Table 3). Surgery was recommended to 2 patients (1.2%) with newly developed lymph node metastasis in the lateral compartment found during follow-up. An increase in size of the carcinoma or the appearance of lymph node metastases was not the main reason of conversion to surgical treatment in most cases. The remaining 47 patients underwent surgical treatment for various other reasons such as patient choice or the enlargement of associated benign nodules. They were all diagnosed as papillary carcinoma by pathological examination, and their TNM classification is summarized in Table 3.

Surgical treatment group

Background of the patients. The TNM classification of patients belonging to the surgical treatment group is summarized in Table 3; no significant difference can be observed between patients who had immediate surgery and those who had surgery after follow-up. We performed a total or near-total thyroidectomy in 276 patients (44.1%), because their carcinomas were multiple and located in both lobes or because associating benign nodules were located in another lobe. For the remaining 350 patients (55.9%), we performed a thyroidectomy of smaller range, such as subtotal thyroidectomy, lobectomy, isthmectomy, or partial lobectomy. Central lymph node dissection was performed in 594 patients (94.9%), and 317 patients (50.7%) also underwent dissection of the lateral compartment. All 626 patients were diagnosed with papillary carcinoma also by postoperative pathologic examination. We dissected the lymph nodes in the lateral

<table>
<thead>
<tr>
<th>Time of follow-up</th>
<th>Total</th>
<th>Size (mm)</th>
<th>Increased</th>
<th>Unchanged</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (beginning of follow-up)</td>
<td>162</td>
<td>6.9 ± 1.8* **</td>
<td>92 (70.8%)</td>
<td>18 (13.8%)</td>
<td></td>
</tr>
<tr>
<td>One year</td>
<td>130</td>
<td>7.0 ± 2.3</td>
<td>20 (15.3%)</td>
<td>90 (62.1%)</td>
<td>24 (16.6%)</td>
</tr>
<tr>
<td>Two years</td>
<td>145</td>
<td>6.8 ± 3.0</td>
<td>31 (21.4%)</td>
<td>92 (62.1%)</td>
<td>22 (14.6%)</td>
</tr>
<tr>
<td>Three years</td>
<td>90</td>
<td>7.8 ± 2.4*</td>
<td>19 (21.1%)</td>
<td>61 (67.8%)</td>
<td>10 (11.1%)</td>
</tr>
<tr>
<td>Four years</td>
<td>72</td>
<td>7.8 ± 2.2**</td>
<td>21 (29.2%)</td>
<td>48 (66.7%)</td>
<td>3 (4.2%)</td>
</tr>
<tr>
<td>Five years or more b</td>
<td>58</td>
<td>7.0 ± 2.4</td>
<td>16 (27.5%)</td>
<td>35 (60.3%)</td>
<td>7 (12.1%)</td>
</tr>
</tbody>
</table>

a The size was compared with that at the beginning of follow-up in each case. Increased: 2 mm or more increase in maximum diameter on ultrasonography. Decreased: 2 mm or more decrease in maximum diameter on ultrasonography.

b Ten years in the longest patients.

*p = 0.0133, **p = 0.0001
compartment when the presence of metastases was preoperatively detected by ultrasound. Otherwise, the range of lymph node dissection depended on the preference of each surgeon. Two patients presented with paralysis of the vocal cords caused by invasion of the tumor to the recurrent laryngeal nerve and they underwent reconstruction of the nerve using the ansa cervicalis to recurrent nerve anastomosis technique (9). The tumors of 5 patients invaded the trachea, and required partial resection of the trachea.

Lymph node metastasis and multiple tumor formation. Lymph node metastasis was pathologically confirmed in 300 patients, accounting for 50.5% of the 594 patients who received lymph node dissection. We performed dissection in the central compartment in all of these patients, and lymph node metastasis was pathologically diagnosed in 258 patients (43.4%). The lateral compartment was dissected in 317 patients and 141 (44.5%) had node metastasis. Of these 141 patients, metastasis had been detected by preoperative ultrasound in only 55 patients (39.0%), and the remaining 86 patients (61.0%) were diagnosed as negative for metastasis in this compartment.

Multiple tumor formation was pathologically confirmed in 269 patients (42.8%). However, it was detected in only 126 patients (47.0%) preoperatively.

Outcome of the patients. Postoperative follow-up has been performed by ultrasonography with or without chest roentgenography more than once per year, the follow-up time averaging 48.7 months (range, 0–120 months). Thus far, 16 of the 626 patients have shown recurrence, accounting for 2.6% of our series. Table 4 shows the sites of recurrence in these patients. Twelve of the 626 patients (1.9%) had recurrence in the lymph node and 4 in the residual thyroid, accounting for 1.1% of the 350 patients not undergoing total or near-total thyroidectomy. No distant metastases to the lung or bone have been detected by roentgenography in any patients. The rate of recurrence was 2.7% at 5 years and 5.0% at 8 years (Fig. 1). No patients have died of the disease.

Discussion

Papillary carcinoma is not a rare disease and is frequently found at autopsy (10–17). Tumors ranging from 3–9.9 mm, which can be detected by ultrasound, were present in 2.3%–5.2% of autopsy studies (10,16,17). Furthermore, Takebe et al. (18) detected papillary carcinomas larger than 3 mm in 3.5% of otherwise healthy women ages 30 years or older by mass screening using ultrasonography and FNAB; 84% were smaller than 15 mm. All of these women underwent surgery and histologically confirmed as having papil-
lary carcinoma, indicating that the prevalence of this disease is 3500 per 100,000 females. On the other hand, studies in Japan and other countries have shown that the prevalence of clinically apparent thyroid carcinoma was much lower, only 2.0–3.8 per 100,000 females (19–21), suggesting that most papillary microcarcinomas remain latent and harmless for their hosts.

On the other hand, previous reports demonstrated that papillary carcinoma even smaller than 10 mm shows frequent lymph node metastasis and multiple tumor formation (3–7). This was the case in our series; more than 40% of patients were positive for lymph node metastasis and multiple tumor formation. Our findings also showed that these metastases and multiple tumor formations are often difficult to detect by ultrasonography.

The question of how to treat asymptomatic papillary microcarcinomas remains. The most important finding in this study is that most patients in the observation group showed no evidence of apparent disease progression during the follow-up period. Of the 141 patients in the surgical treatment group who had lymph node metastasis in the lateral compartment, only 55 (39.0%) were preoperatively diagnosed with metastasis by ultrasound, indicating that the incidence of false-negative results is high for metastasis in the lateral compartment. It is thus suggested that our observation group includes a high percentage of tumors with cervical lymph node metastasis, undetectable by ultrasonography. However, thus far, only 2 patients (1.2%) in the observation group underwent surgery because of lymph node metastasis appeared in the lateral compartment. These findings suggest that papillary microcarcinoma may often be stable for a long period and we may have detected numerous tumors not requiring therapy and recommended unnecessary surgery for these patients, as noted by Black et al. (22). These results suggest that periodic and careful follow-up can be appropriate for most patients with papillary microcarcinoma except for those with the potentially high-risk features mentioned in the Patients and Methods section. It may not be too late for surgeons to recommend surgical treatment when tumors show apparent progression. Such an incidence may not be

### Table 4. Recurrence Sites of Patients After Surgery

<table>
<thead>
<tr>
<th>Lymph node</th>
<th>Number of patients</th>
</tr>
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<tbody>
<tr>
<td>Patients with lymph node dissection (32 patients)</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Dissection of central compartment only (277 patients)</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>Dissected lateral compartment (317 patients)</td>
<td>7 (2.2%)</td>
</tr>
<tr>
<td>Residual thyroid Patients with residual thyroid (350 patients)</td>
<td>4 (1.1%)</td>
</tr>
</tbody>
</table>

*a* Lymph node recurrence was found only in the lateral compartment.

*b* Five cases were ipsilateral lymph node and two were contralateral lymph node not being dissected at surgery.

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![Recurrence rate of papillary microcarcinoma patients who underwent surgery.](image)

**FIG. 1.** The recurrence rate of papillary microcarcinoma patients who underwent surgery.
very high, although further studies with a longer follow-up for a larger number of patients are needed to draw any conclusions.

When we perform surgical treatment, it is important to design the operation. As shown in Table 3, lymph node metastasis (pN1) and multiple tumor formation (pT1b, pT2b, pT4b) were pathologically confirmed in more than 40% of patients who underwent surgery. It is reasonable to dissect lymph nodes in the central compartment routinely, because subsequent surgery for node metastases in this area is not easy. We also should perform dissection of the lateral compartment when metastasis is preoperatively detected. However, in our series, 60.0% of patients with metastasis in the lateral compartment could not be diagnosed preoperatively, indicating that metastatic lymph nodes remain undissected in considerably high incidence in patients without dissection in the lateral compartment. On the other hand, the rate of recurrence in patients without dissection in the lateral compartment was only 1.6% (5 of the 309 patients; see Table 4). Hay et al. (7) also reported the excellent prognosis of microcarcinoma, although they performed modified neck dissection only when the lymph nodes were palpably abnormal. Similarly, multiple tumor formation failed to be detected in 53.0% of patients preoperatively, but the recurrence rate in the residual thyroid was only 1.1% of patients. We therefore hypothesize that many patients have an excellent prognosis, in spite of carcinoma cells possibly residing in the lymph nodes and residual thyroid, indicating that such residual carcinoma may often not be clinically harmful for patients, although longer follow-up is necessary to confirm our hypothesis.

Although papillary microcarcinomas are usually slow growing, some types with an aggressive character and worse prognosis have been reported (7,23–25). In these cases, there are some risk factors such as extracapsular invasion and size of metastatic lymph nodes (23,24), hoarseness caused by recurrent laryngeal nerve palsy (25), age, and postoperative thyroglobulin (26), Ki-67 labeling index, and transforming growth factor (TGF) β3 immunoreactivity (25). If we could accurately evaluate the potentially aggressive character of microcarcinoma preoperatively, it would be a significant help in deciding the indication of surgical treatment for each patient. At present, we consider that it is preferable to evaluate the nature of microcarcinoma by observation without surgery.

In summary, we demonstrated that papillary microcarcinomas can often remain latent with no life-threatening effects on patients, and we can select observation without surgical treatment, although a study with a longer period of follow-up should be performed in order to reach a definite conclusion. Furthermore, studies to evaluate the biologic aggressiveness of each microcarcinoma, especially by ultrasound and FNAB findings as well as pathologic examination, are needed to determine a treatment for patients with no risk.

References


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