

## Long-term Follow-up for Patients with Papillary Thyroid Carcinoma Treated as Benign Nodules

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**Abstract.** *Background:* The recent prevalence of ultrasonography and fine-needle aspiration biopsy (FNAB) has facilitated the detection and diagnosis of papillary thyroid carcinoma. However, there are still cases that are preoperatively misdiagnosed and treated as benign nodules because ultrasonographic and FNAB findings do not provide sufficient evidence for a malignant diagnosis. In this study, we investigated the clinical outcomes of patients with papillary carcinoma that had not been recognized preoperatively. *Patients and Methods:* We investigated the prognoses of 56 patients with papillary carcinoma who underwent thyroidectomy without node dissection under a diagnosis of benign nodules. *Results:* None of the patients underwent further surgery such as completion total thyroidectomy and node dissection after the pathological diagnosis of papillary carcinoma was established. However, to date, only 3 patients (5.3%) showed recurrence 116, 133 and 148 months after the initial surgery, respectively. Two patients showed recurrence in the remnant thyroid and one showed recurrence in the bone. None of the patients have died of thyroid carcinoma. *Conclusion:* Papillary carcinomas misdiagnosed as benign nodules on ultrasonography and FNAB are indolent and very slow-growing. Immediate further surgery is not needed for such cases, even if they were resected as benign nodules at the initial surgery.

Papillary carcinoma is the most common histological type of thyroid malignancy originating from follicular cells. Although cases showing certain clinicopathological features such as clinically apparent node metastasis, large tumor and massive extrathyroid extension are progressive with a dire prognosis (1-7), most cases show a mild characteristic and grow slowly.

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Ultrasonography and fine-needle aspiration biopsy (FNAB) are useful tools for diagnosing papillary carcinoma (8).

When a tumor is diagnosed as papillary carcinoma, thyroidectomy with lymph node dissection is performed. The extent of thyroidectomy and node dissection varies according to the progression of disease as well as the national standard for such surgeries. In Europe and the United States, total thyroidectomy with or without central node dissection followed by radioiodine therapy is widely performed, unless node metastasis in the lateral compartment was detected preoperatively. However, in Japan, since the use of radioiodine is strictly limited by law, thyroidectomy of limited range such as subtotal thyroidectomy or lobectomy with isthmectomy along with prophylactic modified radical neck dissection have been more frequently adopted.

Papillary carcinoma is occasionally misdiagnosed as benign nodules when ultrasonographic and FNAB findings do not show adequate evidence for diagnosis of malignancy. Most such tumors are then resected as benign nodules by thyroidectomy with a limited range without lymph node dissection. Thereafter, these tumors are diagnosed as papillary carcinoma by postoperative pathological examination. To date, there have not been any studies regarding the biological characteristics of papillary carcinomas misdiagnosed as benign nodules nor whether further surgery, such as completion of total thyroidectomy and lymph node dissection, is necessary to improve the prognosis of patients with these lesions. In this study, therefore, we investigated the outcomes of patients on long-term follow-up, after papillary carcinomas were misdiagnosed and resected as benign nodules.

### Patients and Methods

*Patients.* Since 1981, our department has performed FNAB to diagnose thyroid nodules. Ultrasonography was introduced in 1986, which facilitated the detection of small thyroid nodules more easily, but FNAB was still performed blindly. Ultrasonography-guided FNAB was adopted in 1992, facilitating accurate diagnosis of small, non-palpable nodules, including papillary microcarcinoma.

Between 1987 and 1995, 1730 patients underwent initial and curative surgical treatment with papillary carcinoma at Kuma Hospital. Patients with inadequate postoperative follow-up and those who underwent surgery with an atypical surgical design were excluded from the series. Furthermore, incidental carcinomas that had not been preoperatively detected, because the lesion was of small size, but were confirmed by postoperative pathological examination were also excluded from our series. Of these, 1663 (95.6%) had been diagnosed as having, or suspected of having, papillary carcinoma before surgery based on ultrasonography and FNAB findings. Thyroidectomy and lymph node dissection were performed in 1659 of these patients. The remaining 4 underwent thyroidectomy only without node dissection because surgeons doubted whether FNAB findings had definitely diagnosed malignancy and intraoperatively evaluated the lesion as a benign nodule. Sixty-seven patients (3.9%) were not diagnosed as having papillary carcinoma but rather adenomatous goiter or follicular tumor based on ultrasonographic and FNAB findings. Fifteen of these patients underwent surgery for papillary carcinoma because surgeons intraoperatively suspected the tumors of being papillary carcinoma, but the remaining 52 underwent surgery for benign nodules.

In total, 56 (4 plus 52) patients were enrolled in this study. Five patients underwent surgery after the introduction of ultrasonography-guided FNAB in 1992 and the remaining 51 underwent surgery before 1992. Other benign nodules such as adenomatous nodule, adenomatous goiter and follicular adenoma coexisted in 12 patients and one patient had Basedow's disease.

In contrast, 1674 patients (1659 plus 15) underwent thyroidectomy and lymph node dissection. Bilateral and unilateral modified radical neck dissections were performed for 207 and 1267 patients, respectively. The remaining 200 patients underwent central node dissection only.

We compared these two groups for various characteristics and patient survival.

*Postoperative follow-up.* None of the 56 patients underwent further surgery such as completion of total thyroidectomy and lymph node dissection after diagnosis of papillary carcinoma on postoperative pathological examination. All patients were followed up once or twice per year by US, chest roentgenography and/or computed tomography (CT) to screen for recurrence in lymph nodes or distant organs. Furthermore, patients who were postoperatively referred to other hospitals near their residences were sent questionnaires to obtain data on cause-specific survival. Follow-up time for disease-free survival averaged 117.0 months (6-209 months) and that for cause-specific survival averaged 157.5 months (47-209 months).

*Statistical analyses.* Chi-square analysis was employed for comparing the two groups with variables. The Kaplan-Meier curve and log rank test were adopted for analysis of patient survival.

## Results

The difference in clinicopathological features was investigated between 56 patients diagnosed and treated as having benign nodules and 1674 patients treated for papillary carcinoma. The results are summarized in Table I.

Table I. Background and clinicopathological features of 1730 papillary carcinoma patients (%).

|                          | Patients treated as having benign nodules (56 patients) | Patients treated for papillary carcinoma (1674 patients) | p-value |
|--------------------------|---|--|---------|
| Gender                   |   |  |         |
| Male                     | 3 (5.4)   | 118 (7.0)  |         |
| Female                   | 53 (94.6)   | 1556 (93.0)  | N.S.    |
| Age (years)              |   |  |         |
| >45                      | 25 (44.6)   | 1022 (61.1)  |         |
| ≤45                      | 31 (55.4)   | 652 (38.9)   | 0.0175  |
| Tumor size (cm)          |   |  |         |
| >4                       | 11 (19.6)   | 185 (11.1)   |         |
| ≤4                       | 45 (80.4)   | 1489 (88.9)  | 0.0482  |
| N classification         |   |  |         |
| N0                       | 56 (100)  | 1410 (84.1)  |         |
| N1a                      | 0   | 34 (20.2)  |         |
| N1b                      | 0   | 230 (13.7)   | 0.0055  |
| Range of thyroidectomy   |   |  |         |
| Total                    | 3 (5.4)   | 884 (52.8)   |         |
| Subtotal                 | 8 (14.3)  | 184 (11.0)   |         |
| Lobectomy or isthmectomy | 45 (80.4)   | 606 (36.2)   | <0.0001 |
| Extrathyroid extension   |   |  |         |
| None                     | 55 (98.2)   | 1019 (60.9)  |         |
| Minimal                  | 1 (1.8)   | 439 (26.2)   |         |
| Massive                  | 0   | 216 (12.9)   | <0.0001 |
| pStage                   |   |  |         |
| I                        | 43 (76.8)   | 819 (48.9)   |         |
| II                       | 6 (10.7)  | 52 (3.1)   |         |
| III                      | 7 (12.5)  | 220 (13.1)   |         |
| IVA                      | 0   | 583 (34.8)   | <0.0001 |
| Carcinoma recurrence     |   |  |         |
| Yes                      | 3 (5.4)   | 186 (10.8)   |         |
| No                       | 53 (94.6)   | 1488 (89.2)  |         |
| Death due to carcinoma   |   |  |         |
| Yes                      | 0   | 23 (1.4)   |         |
| No                       | 56 (100)  | 1651 (98.7)  |         |

N.S.: not significant.

Patients treated as having benign nodules were younger than those treated for papillary carcinoma. Tumor size was larger in patients treated as benign nodules. Lymph node metastasis was preoperatively detected by imaging tests in 264 patients (33.9%) treated for papillary carcinoma, while none of the 56 patients treated as having benign nodules showed lymph nodes suspected of metastasis. Total thyroidectomy was performed in only 3 patients (5.4%) treated as having benign nodules because these patients had nodules in both lobes, but 884 (52.8%) treated for papillary carcinoma underwent total thyroidectomy. Minimal extrathyroid extension, extension only to the sternohyoid muscle or perithyroid fat tissue, was observed in only 1 patient (1.8%) treated as having benign nodules, while the

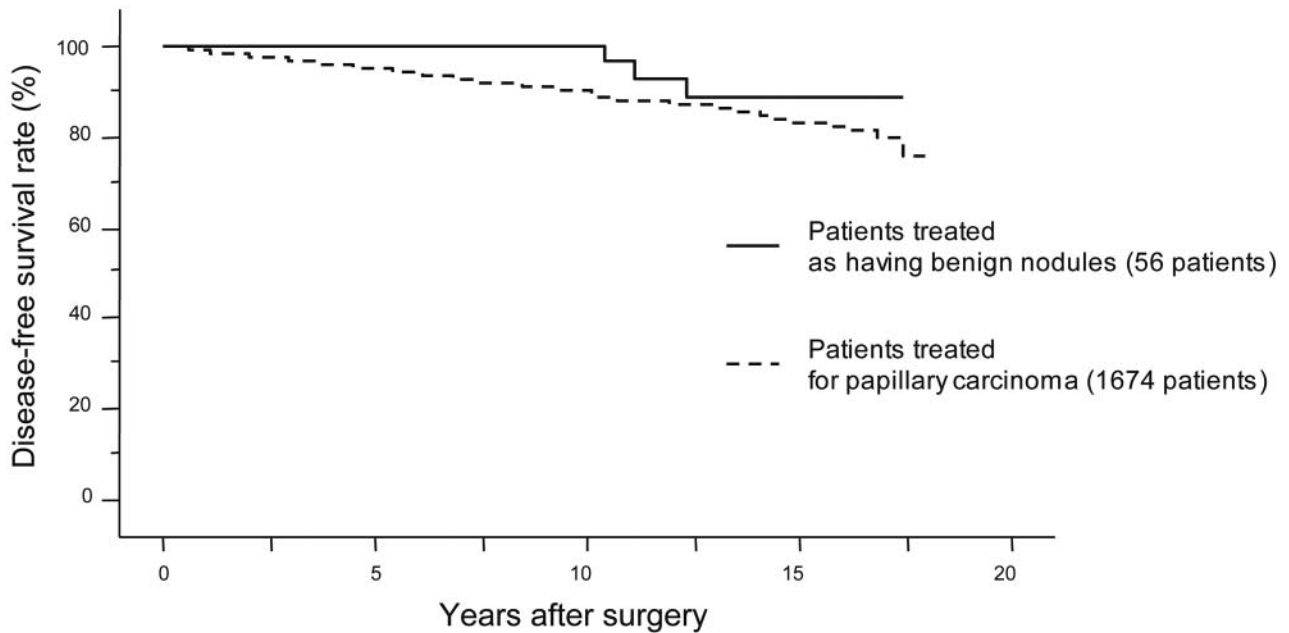


Figure 1. Kaplan-Meier curves of disease-free survival of papillary carcinoma patients treated as having benign nodules and those treated for papillary carcinoma.

remaining 55 patients did not show any extrathyroid extension. However, 216 patients (12.9%) treated for papillary carcinoma showed massive extension, extension to the recurrent laryngeal nerve, esophagus, trachea, sternohyoid muscle and other structures and 439 (26.2%) showed minimal extension. Regarding pStage, 583 patients (34.8%) treated for papillary carcinoma were classified as pStage IVA, but none of the patients treated as having benign nodules were classified as pStage IVA.

As indicated above, none of the patients treated as having benign nodules underwent further surgical treatment, such as completion of total thyroidectomy and lymph node dissection after pathological diagnosis of papillary carcinoma. However, to date, only 3 patients (5.3%) treated as having benign nodules have shown recurrence and the incidence was lower than that in patients treated for papillary carcinoma, 10.8%. Two of these patients showed recurrence in the remnant thyroid 133 months and 148 months after the initial surgery. One patient underwent reoperation but the other has been followed without evidence of carcinoma progression. The remaining patient showed recurrence in the bone 116 months after surgery; this patient was still alive at the time of the last follow-up, 132 months after surgery. None of the patients in this group showed recurrence in locoregional lymph nodes. Figure 1 indicates the Kaplan-Meier survival curves of these patients and shows there was no significant difference between the two groups.

To date, although two patients treated as having benign nodules have died of diseases unrelated to thyroid carcinoma 109 and 182 months after surgery, none have died of thyroid carcinoma. However, 23 patients (1.4%) treated for papillary carcinoma have died of thyroid carcinoma. Figure 2 indicates the Kaplan-Meier curves of cause-specific survival for the two groups. Since none of the patients treated as having benign nodules have died of carcinoma, *p*-values could not be calculated.

## Discussion

This is the first study investigating the long-term clinical outcomes of patients with papillary carcinoma treated as benign nodules. Most papillary carcinomas can be preoperatively diagnosed by clinical features such as palpable hard mass, ultrasonographic and FNAB findings. The 56 patients treated as having benign nodules in our series lacked these features, except for 4 patients suspected of papillary carcinoma on FNAB findings. Furthermore, none of these patients showed clinicopathological features reflecting biologically aggressive behaviors such as preoperatively detected lymph node metastasis (N1a and N1b) or massive extrathyroid extension (1). Age is also known to be a prognostic factor for papillary carcinoma. Indeed, in UICC/AJCC classification, all patients aged younger than 45 years are classified as stage I unless they have distant

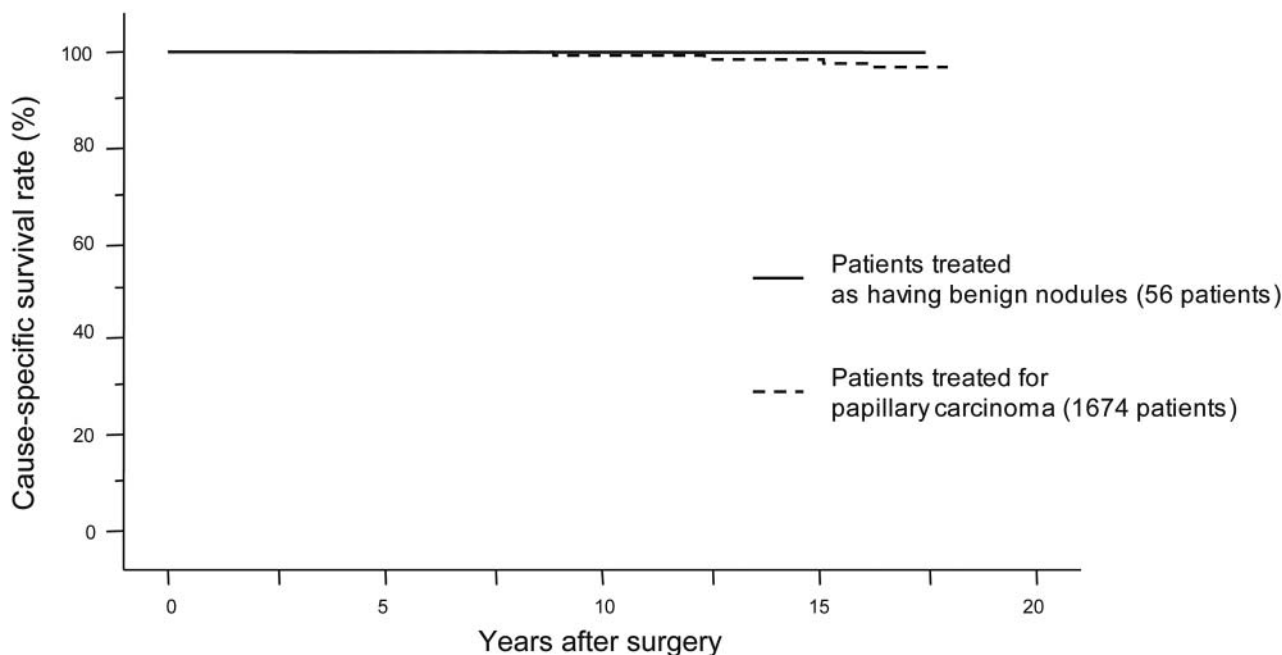


Figure 2. Kaplan-Meier curves of cause-specific survival of papillary carcinoma patients treated as having benign nodules and those treated for papillary carcinoma.

metastasis (9). Patients whose condition was treated as benign nodules were significantly younger than those treated as papillary carcinoma, which was not discrepant with the above findings. However, tumors of patients treated as having benign nodules were larger than those of patients treated for papillary carcinomas. Tumor size also has a prognostic value and, in particular, tumors larger than 4 cm represent a significantly worse disease-free survival (2). Therefore, we can conclude that papillary carcinoma treated as benign nodules had less aggressive clinicopathological characteristics except for tumor size.

The lack of most characteristics reflecting aggressive tumor behaviors in patients treated as having benign nodules predicts a good prognosis. Indeed, none of our 56 patients treated as having benign nodules died of carcinoma (Figure 2). Furthermore, although there were no additional surgical treatments such as completion of total thyroidectomy and lymph node dissection, only 3 patients showed carcinoma recurrence, including one showing distant metastasis. Good prognoses in patients treated as having benign nodules could also be confirmed using Kaplan-Meier curves (Figure 1).

We previously demonstrated that although the positive predictive value and specificity of ultrasonographic diagnosis of node metastasis were high at over 90%, its sensitivity was low, less than 30%. Furthermore, the

negative predictive value was only 42%, indicating that node metastasis would be expected in more than 50% of papillary carcinoma without ultrasonography-detectable node metastasis, if node dissection were performed (1, 3). It is therefore suggested that these 56 patients also had node metastasis at a considerably high incidence. However, interestingly, none of the patients showed recurrence in the lymph nodes, indicating that even if there were metastatic nodes undetectable on ultrasonography, these lesions remained latent and did not become clinically apparent possibly because of their extremely slow-growing characteristic.

In our hospital, FNAB and ultrasonographic examination have been performed since 1981 and 1986, respectively, which definitely facilitated detection and diagnosis of papillary carcinoma. However, when FNAB was being performed blindly, its diagnostic accuracy was still limited. Since 1992, ultrasonography-guided FNAB has been performed (8), which facilitates a more accurate diagnosis of carcinoma because cells can be more accurately aspirated from small non-palpable tumors. Indeed, only 5 cases were misdiagnosed and underwent surgery as benign nodules between 1992 and 1995, while 51 underwent surgery as benign nodules between 1987 and 1991. Definitely, the incidence of misdiagnosis has been reduced by the introduction of ultrasonography-guided FNAB.

## Conclusion

We demonstrated that papillary carcinomas misdiagnosed as benign nodules by ultrasonographic and FNAB findings were usually indolent and slow-growing and that the incidence of recurrence was very low, even if the lesions underwent resection as benign nodules. Therefore, in such cases, routine follow-up without additional surgery should be appropriate.

## References

- 1 Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K and Miyauchi A: Ultrasound-detectable and anatomopathologically-detectable node metastasis in the lateral compartment as indicators of worse relapse-free survival in patients with papillary thyroid carcinoma. *World J Surg* 29: 917-920, 2005.
- 2 Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K and Miyauchi A: Prognostic significance of extrathyroid extension of papillary thyroid carcinoma: massive but not minimal extension affects the relapse-free survival. *World J Surg* 30: 780-786, 2006.
- 3 Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K and Miyauchi A: Preoperative ultrasonographic examination for lymph node metastasis is useful when designing lymph node dissection for papillary microcarcinoma. *World J Surg* 28: 498-501, 2004.
- 4 Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K and Miyauchi A: Minimal extrathyroid extension does not affect the relapse-free survival of patients with papillary thyroid carcinoma measuring 4 cm or less over the age of 45. *Surg Today* 36: 12-18, 2006.
- 5 Russell MA, Gilbert EF and Jaescheke WF: Prognostic features of thyroid cancer. A long-term follow-up of 68 cases. *Cancer* 36: 553-559, 1975.
- 6 Moreno-Egea A, Rodriguez-Gonzalez JM and Sola-Perez J: Multivariate analysis of histopathological features as prognostic factors in patient with papillary thyroid carcinoma. *Br J Surg* 82: 1092-1094, 1995.
- 7 Bellantone R, Lombardi CP and Boscherini M: Prognostic factors in differentiated thyroid carcinoma: a multivariate analysis of 234 consecutive patients. *J Surg Oncol* 82: 1092-1094, 1998.
- 8 Yokozawa T, Miyauchi A, Kuma K and Sugawara M: Accurate and simple method of diagnosing thyroid nodules by the modified technique of ultrasound-guided fine needle aspiration biopsy. *Thyroid* 5: 141-145, 1995.
- 9 Sobin LH, Wittekind CH (eds.). UICC: TNM classification of malignant tumors, 6th ed. New York: Wiley-Liss, 2002.

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