

An Observational Trial for Papillary Thyroid Microcarcinoma in Japanese Patients

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Abstract

Background The recent development and spread of ultrasonography and ultrasonography-guided fine needle aspiration biopsy (FNAB) has facilitated the detection of small papillary microcarcinomas of the thyroid measuring 1 cm or less (PMC). The marked difference in prevalence between clinical thyroid carcinoma and PMC detected on mass screening prompted us to observe PMC unless the lesion shows unfavorable features, such as location adjacent to the trachea or on the dorsal surface of the thyroid possibly invading the recurrent laryngeal nerve, clinically apparent nodal metastasis, or high-grade malignancy on FNAB findings. In the present study we report comparison of the outcomes of 340 patients with PMC who underwent observation and the prognosis of 1,055 patients who underwent immediate surgery without observation.

Methods Between 1993 and 2004, 340 patients underwent observation and 1,055 underwent surgical treatment without observation. These 1,395 patients were enrolled in the present study. Observation periods ranged from 18 to 187 months (average 74 months).

Results The proportions of patients whose PMC showed enlargement by 3 mm or more were 6.4 and 15.9% on 5-year and 10-year follow-up, respectively. Novel nodal

metastasis was detected in 1.4% at 5 years and 3.4% at 10 years. There were no factors related to patient background or clinical features linked to either tumor enlargement or the novel appearance of nodal metastasis. After observation 109 of the 340 patients underwent surgical treatment for various reasons, and none of those patients showed carcinoma recurrence. In patients who underwent immediate surgical treatment, clinically apparent lateral node metastasis (N1b) and male gender were recognized as independent prognostic factors of disease-free survival.

Conclusions Papillary microcarcinomas that are not associated with unfavorable features can be candidates for observation regardless of patient background and clinical features. If there are subsequent signs of progression, such as tumor enlargement and novel nodal metastasis, it would not be too late to perform surgical treatment. Even though the primary tumor is small, careful surgical treatment including therapeutic modified neck dissection is necessary for N1b PMC patients.

Introduction

Papillary carcinoma is the most common malignancy originating from the thyroid. Usually, papillary carcinoma is indolent and grows slowly, although cases having certain biological characteristics, such as clinically apparent node metastasis in the lateral compartment (N1b in the International Union Against Cancer [UICC] tumor node metastasis [TNM] classification [1]) and massive extrathyroid extension (pT4[1]) are progressive [2–4]. Papillary carcinoma measuring 1.0 cm or less is defined as papillary microcarcinoma (PMC) by the World Health Organisation (WHO) classification. Formerly, detection of

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PMC without clinically apparent lymph nodal and/or distant metastasis was exceedingly difficult because PMC is rarely palpable. Therefore, in the past, PMC could be classified into three categories based on the circumstances of detection: (1) latent PMC, which are detected in autopsy specimens; (2) occult PMC, which are discovered as the origin of lymph node and/or distant metastasis; and (3) incidental PMC, which are detected on pathological examination of surgical specimens resected for other diseases.

Recently, however, screening of the thyroid and carotid artery by ultrasonography has facilitated the detection of small thyroid nodules measuring a minimum of 3 mm. These PMC can be diagnosed on cytologic examination of specimens obtained by ultrasonography-guided fine-needle aspiration biopsy (FNAB) [5]. Takebe et al., reported the detection of papillary carcinomas in 3.5% of otherwise healthy women aged 30 years or older by ultrasonography performed as a screening for breast and thyroid cancer and ultrasonography-guided FNAB, noting that 75% of these lesions measured 1.5 cm or smaller [6]. This incidence was not discrepant with that of latent PMC measuring 3.0–9.9 mm in autopsy specimens, which have been reported to range from 0.5 to 5.2% [7–9]. In contrast, however, the prevalence of clinical thyroid papillary carcinoma was 1.9–11.7 per 100,000 females of all ages [3, 10], which is about 1,000 times lower than that of PMC detected on ultrasonography. The marked difference between these prevalences suggests that PMC rarely grow and become clinically apparent, prompting the question of whether immediate surgery is mandatory for all PMC detected on mass screening, although PMC is also known to show multicentricity in 15–44% of lesions and regional lymph node metastasis in 14–64% of lesions [11–20].

Based on the above findings, we hypothesized that most PMC do not require immediate surgical treatment and that affected patients can be followed by observation in the outpatient clinic. In 1993, we initiated an observational trial of PMC. When we diagnosed nodules measuring 1 cm or less as papillary carcinoma by ultrasonography-guided FNAB, we propose two therapeutic alternatives, observation without surgery or surgical treatment, and we allowed the patient to choose. In 2003, we published our first report of the outcome of 162 patients with PMC, which indicated that over 70% of tumors did not change from their initial size and that novel lymph node metastasis appeared in only 1.2% of patients during follow-up (average follow-up was 47 months [range: 18–113 months]) [21]. In a review article published in 2007, we demonstrated that only 6.7% of tumors show enlargement by 3 mm or more during a 5-year follow-up [22]. In the present study, we present our most recent data from observation of PMC patients as a follow-up report.

Patients and methods

Diagnosis of PMC and recommendation of observation

Diagnosis of PMC and recommendation of observation were performed as described in our previous reports [20–23]. Briefly, when patients are diagnosed with nodules measuring 1 cm or less that showed as papillary carcinoma on ultrasonography-guided FNAB, we presented two therapy options: observation and surgical treatment. However, when the PMC demonstrated such unfavorable features (1) location adjacent to the trachea; (2) location on the dorsal surface of the thyroid lobe, possibly invading the recurrent laryngeal nerve; (3) FNAB findings suggesting high-grade malignancy; (4) presence of regional node metastasis; and/or (5) presence of signs of progression during follow-up, we recommend surgical treatment without observation. Regional lymph node metastasis was diagnosed on ultrasonography based on criteria described elsewhere [20, 21]. When patients choose observation, PMC is followed by ultrasonography once or twice per year to determine whether the tumor size has changed or lymph node metastasis newly appears. Between 1993 and 2004, 340 patients were diagnosed with PMC by ultrasonography-guided FNAB and underwent observation for 18 months or longer. These patients were enrolled in this study as the observation group. They consisted of 314 females and 26 males and their follow-up periods ranged from 18 to 187 months (average: 74 months). Twenty-seven patients underwent thyroid stimulating hormone (TSH) suppression treatment to the low normal or less than normal range by L-thyroxine based on the discretion of attending physicians. We routinely measured serum thyroglobulin at every follow-up. Antithyroid antibodies were positive for 93 patients. For the purposes of this study, tumor enlargement was defined by an increase in tumor size of 3 mm or more compared with the size at initiation of observation, but only when there was no change or a further increase on the next examination. We established this parameter because, in our experience, + 2 mm has been recognized as an observer variation. To date, 109 patients (102 females and 7 males) (32.1%) have undergone surgical treatment for various reasons. Intervals from initiation of observation to surgery ranged from 18 to 175 months (average: 51 months). Postoperative follow-up has included ultrasonography and chest roentgenography or CT scan more than once per year. Postoperative follow-up averaged 76 months (range: 1–198 months).

Immediate surgical treatment group

Between 1993 and 2004, 1,055 patients underwent surgery for PMC without follow-up. These patients were enrolled

in this study as the immediate surgical treatment group. Two patients with distant metastasis at diagnosis were excluded from the series. This patient group then consisted of 1,059 patients, 964 females and 95 males whose age ranged from 15 to 84 years (average: 52.0 years). After surgery, these patients were followed in our outpatient clinic in the same manner as the 109 patients of the observation group. Follow-up averaged 76 months (range: 1–183; months). Radioiodine whole body scan using 3–13 mCi radioiodine was performed for 52 patients, none of whom showed abnormal uptake except in the thyroid bed.

Statistical analyses

The Kaplan–Meier method and log-rank test were adopted to analyze time-dependent variables. The Cox regression model was also used for multivariate analysis. All analyses were performed using StatView-J 5.0. A *p* value less than 0.05 was regarded as significant.

Results

Outcome of PMC patients in observation group

Between 1993 and 2004, 340 patients underwent observation for periods ranging from 18 to 187 months (average 74 months). As indicated above in “Patients and methods” section, we made a judgment of tumor enlargement when the size increased by 3 mm or more compared to the size at initiation of observation and the increased size did not change or showed a further increase on the next examination. To date, PMC of 31 patients (9.1%) showed enlargement based on our criteria. Figure 1 shows the proportion of patients showing enlargement of PMC. On 5-year and 10-year follow-up, 6.4 and 15.9% of patients showed enlargement, respectively.

Seventeen patients (5.0%) were diagnosed as having familial papillary carcinoma, because they had one or more first-degree relatives who had undergone surgical treatment for papillary or follicular carcinoma in our hospital or other hospitals [24]. However, enlargement was not related to whether patients had familial or non-familial papillary carcinoma (Fig. 2a). We investigated the relationship between size enlargement and other various backgrounds of patients and clinical features such as gender, age, tumor size at diagnosis, multicentricity, and TSH suppression, but none of these parameters were related to enlargement (Fig. 2b–f). Although carcinomas of patients aged 45 years or younger tended to enlarge, the difference was not significant ($p = 0.0624$). Furthermore, tumor enlargement was not linked to change in serum thyroglobulin level or the presence of antithyroid antibodies (data not shown).

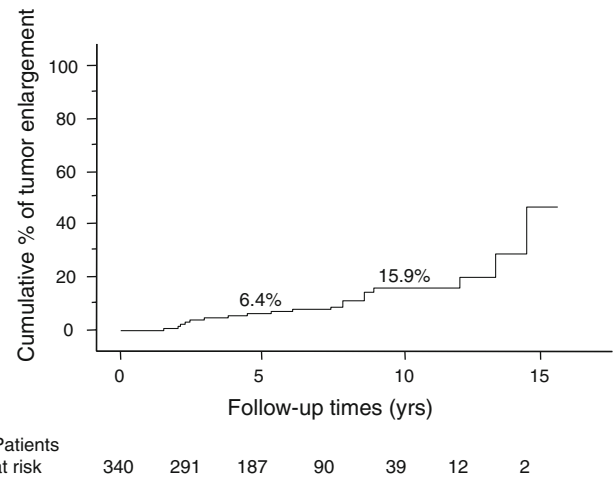


Fig. 1 Proportion of patients whose papillary microcarcinoma (PMC) showed enlargement by 3 mm or more

To date, 7 patients (2.1%) have shown the novel appearance of lymph node metastasis. All new metastases appeared in the lateral compartment ipsilateral to the primary lesion and were diagnosed on ultrasonography, ultrasonography-guided FNAB, and thyroglobulin measurement of wash-out from the needle used for FNAB [25]. As shown in Fig. 3, the proportion of patients showing novel node metastasis was 1.4 and 3.4% at 5-year and 10-year follow-up, respectively. None of the clinicopathological features described here were related to the novel appearance of lymph node metastasis (data not shown).

Of 340 patients, 109 (32%) underwent surgical treatment after observation. Table 1 summarizes the reasons for surgical treatment for 109 patients. The leading reason for surgery was tumor enlargement (32 patients). However, in 17 of those 32 patients, the tumor enlargement leading to operation was not based on the criteria of this study. Conversely, as indicated above, 31 patients were judged as showing carcinoma enlargement according to our criteria and 18 of these patients underwent surgery. Two of the 18 also showed novel appearance of lymph node metastasis. The remaining 13 were continuously followed without surgery, and tumor size was noted to decrease in 7 of these 13 patients. Novel appearance of lymph node metastasis was observed in 7 patients. Surgical treatment was recommended for these patients and 5 underwent surgery. However, the remaining 2 refused surgery and discontinued outpatient consultations. Seventeen patients underwent surgical treatment because of the location of tumor at the dorsal surface after observation. Four of these patients had been followed without diagnosis of malignancy and were recommended for immediate surgical treatment after the diagnosis of PMC. The remaining 13 were diagnosed as having PMC from the beginning but surgical treatment was recommended after a change in the policy of the attending

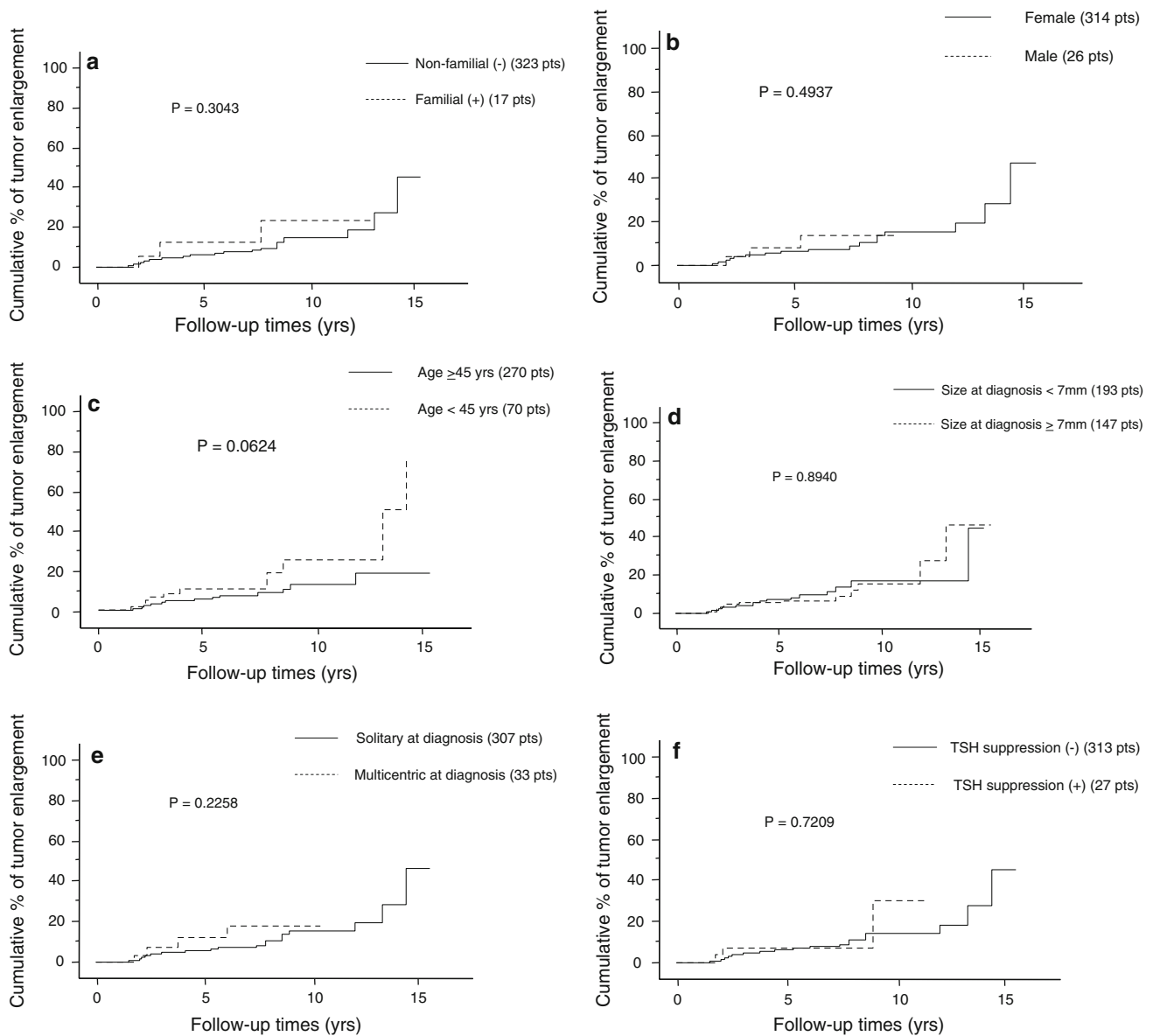


Fig. 2 **a** Proportion of patients with familial or non-familial PMC showing enlargement by 3 mm or more. **b** Proportion of male and female patients whose PMC showed enlargement by 3 mm or more. **c** Proportion of patients aged 45 years or older and those younger than 45 years whose PMC showed enlargement by 3 mm or more. **d** Proportion of patients whose PMC measured 7 mm or larger and

those whose PMC was smaller than 7 mm at diagnosis and subsequently showed enlargement by 3 mm or more. **e** Proportion of patients whose solitary PMC and multiple PMC at diagnosis showed enlargement by 3 mm or more. **f** Proportion of patients whose PMC with thyroid stimulating hormone (TSH) suppression and without TSH suppression showed enlargement by 3 mm or more

physicians. Twelve patients underwent surgery after observation at their choice. Furthermore, one patient, a 15-year-old, was later diagnosed as having familial carcinoma and 7 others whose carcinomas were suspected of having multicentricity were recommended for and underwent surgery. The decision to proceed to operation in these 8 cases was not based on our present indications for surgery.

The extent of thyroidectomy and lymph node dissection in the 109 patients from the observation group who proceeded to operation is summarized in Table 2. The extent

of resection in 2 patients is unknown because their surgery was performed at other hospitals. None of these patients showed carcinoma recurrence after surgery (average follow-up period: 76 months).

Outcome of PMC patients in the immediate surgical treatment group

We investigated the clinical outcomes of 1,055 patients with PMC in the immediate surgical treatment group. The

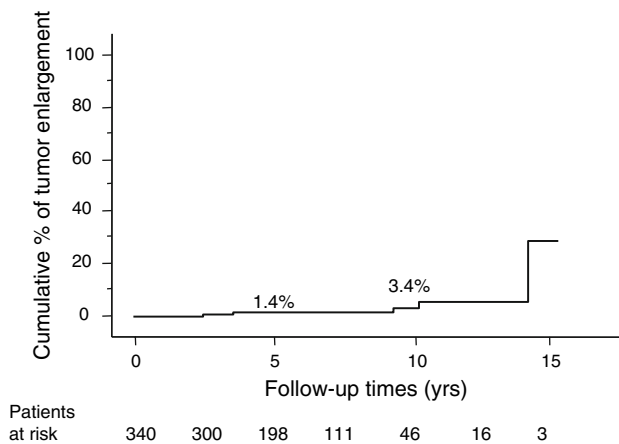


Fig. 3 Proportion of patients whose PMC showed the novel appearance of lymph node metastasis

Table 1 Reasons for surgical treatment in 109 patients with papillary microcarcinoma of the thyroid who initially underwent observation

Later diagnosed as having familial carcinoma ^a	1 patient
Tumor enlargement	32 patients ^b
Young age ^a	1 patient
Suspicion of multicentricity ^a	7 patients ^c
Tumor location near dorsal surface	17 patients ^d
Patients' choice	12 patients
Novel appearance of lymph node metastasis	5 patients
Coexistence of other thyroid diseases	10 patients
Unknown	25 patients

^a They do not meet our criteria in the present study

^b Seventeen patients were not recognized as showing tumor enlargement under the criteria for enlargement used in the present study

^c One patient also showed tumor enlargement

^d Including 4 patients who had been followed without diagnosis of PMC, who underwent immediate surgical treatment at diagnosis

extent of thyroidectomy and lymph node dissection is summarized in Table 3. To date, 32 patients showed carcinoma recurrence during postoperative follow-up. Table 4 summarizes organs in which PMC showed recurrence. The organ to which carcinoma most frequently recurred was the

lymph node. We then investigated the prognostic implications of various clinicopathological parameters and patient background factors. As shown in Fig. 4a, patients with clinically apparent lateral node metastasis (N1b) showed significantly worse disease-free survival (DFS) than those with clinically apparent central node metastasis (N1a) or not having clinically apparent metastasis (N0) ($p < 0.0001$). The DFS of patients with N0 did not differ from that of patients with N1a. Male gender ($p < 0.0001$) (Fig. 4b) and pathologically confirmed lymph node metastasis (pN1) ($p = 0.0004$) also predicted a worse DFS. Our series included 25 patients (2.4%) having PMC with massive extrathyroid extension to the recurrent laryngeal nerve, trachea or esophagus, but none of these patients showed recurrence. Other clinicopathological features, such as age and multicentricity, did not affect DFS of patients (data not shown). We performed multivariate analysis for three features that did show prognostic significance on univariate analysis. N1b and male gender were recognized as independent prognostic factors for DFS (Table 5).

To date, two patients have died of carcinoma 79 and 94 months after the initial operation. Both patients were classified as having clinically apparent lateral node metastasis at presentation, and one also showed metastasis also in the mediastinal compartment.

Comparison between Rate of Novel Appearance of LN Metastasis in Patients Undergoing Observation and Recurrence Rate to the LN in Patients with N0 PMC Undergoing Immediate Surgical Treatment

Of 1,055 patients in the immediate surgical treatment group, 909 did not show clinically apparent lymph node metastasis in the central or lateral compartments (N0). Lymph node dissection was performed for 815 patients [central node dissection only for 525 and prophylactic modified neck dissection (MND) for 290]. To date, 5 of 525 patients who underwent central node dissection showed recurrence to lymph nodes in the lateral compartment. Of 290 patients who underwent MND, 4 showed recurrence to a lateral compartment (3 on the contralateral side and 1 in the ipsilateral compartment). As indicated

Table 2 Extent of thyroidectomy and lymph node dissection of 109 patients who underwent surgical treatment after observation

	Thyroidectomy	Lymph node dissection	
Total or near total	48 (44.0%)	CND only	79 (72.5%)
Subtotal	7 (6.4%)	Unilateral MND	26 (23.9%)
Lobectomy with isthmectomy	47 (43.1%)	Bilateral MND	2 (1.8%)
Isthmectomy	5 (4.6%)	Unknown ^b	2 (1.8%)
Unknown ^a	2 (1.8%)		

CND complete radical neck dissection, MND modified radical neck dissection

^a These two patients underwent surgery at other hospitals

Table 3 Extent of thyroidectomy and lymph node dissection of 1,055 patients in the immediate surgical treatment group

	Thyroidectomy	Lymph node dissection	
Total or near total	432 (40.9%)	CND only	536 (50.8%)
Subtotal	101 (9.6%)	Unilateral MND	402 ^a (38.1%)
Lobectomy with isthmectomy	490 (46.4%)	Bilateral MND	23 (2.2%)
		Not done	94 (8.9%)
Isthmectomy	25 (2.4%)		
Partial lobectomy	7 (0.7%)		

^a One patient also underwent dissection of the mediastinal compartment

Table 4 Recurrence in 32 patients^a (3.0%)

Lymph node	26 (2.5%)
Previously dissected compartments	11
Compartments that had not been dissected	13
Both compartments	2
Locoregional organs	
Thyroid	6 (0.6%)
Others	2 (0.2%)
Distant organs	
Lung	1 (0.1%)
Bone	1 (0.1%)

^a Three patients showed recurrence in two or more organs

Table 5 Multivariate analysis regarding disease-free survival (DFS) of PMC patients

Variables	<i>p</i> values	Hazard ratio (95% confidence interval)
N1b	0.0003	4.46 (2.00–10.00)
Male gender	0.0255	2.59 (1.12–5.95)
pN1	0.1283	2.08 (0.81–5.38)

above, 7 patients in the observation group showed novel lymph node metastasis during follow-up, and all of those lesions were in the lateral compartment ipsilateral to the primary lesion. We compared the rate of novel appearance of nodal metastasis or recurrence to the lymph node in these three subsets. As shown in Fig. 5, the rate of novel appearance of nodal metastasis in the observation group did not differ from that of recurrence to the lymph node in the immediate surgical treatment group. Furthermore, we could not find any significant difference in the rate of recurrence to the lymph node between patients who underwent central node dissection only and those who underwent prophylactic MND.

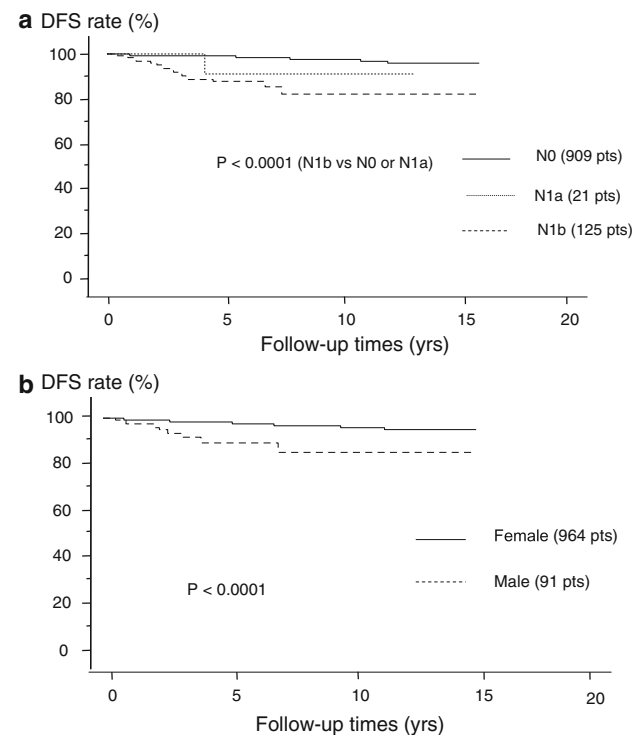


Fig. 4 **a** Kaplan–Meier curves for disease-free survival (DFS) of PMC patients with N1b, N1a, and N0. **b** Kaplan–Meier curves for DFS of male and female patients with PMC

Discussion

This report is a continuation of our observation trial for PMC in patients without any unfavorable features and the prognosis for PMC patients who have undergone operation either immediately after diagnosis or after a period of observation. In this study, we enrolled 340 patients who were diagnosed as having PMC between 1992 and 2004 and subsequently underwent observation without immediate surgical treatment. The average follow-up period increased to 74 months, significantly longer than that in previous studies. However, the rate of carcinoma enlargement was 6.4% at 5-years follow-up, which was similar to that in our previous reports [22, 23]. At 10 years, 15.9% of tumors demonstrated enlargement, but the number of patients at risk at 10 years remained low at 39, indicating

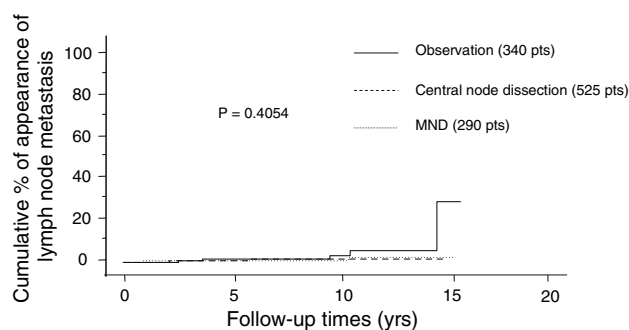


Fig. 5 Proportion of patients whose PMC showed novel appearance of lymph node metastasis during observation, those who underwent central node dissection only and those who underwent prophylactic modified neck dissection (MND) in the immediate surgical group showing recurrence to the node

that the incidence could change with further increases in the number of patients who have been observed for a long time. We also demonstrated the results of the novel appearance of lymph node metastasis during observation: 1.4% at 5 years and 3.4% at 10 years, indicating that the incidence is lower than enlargement of primary tumor.

In our observation series, 109 patients went on to surgical treatment after observation for various reasons. The most common reason was recorded as tumor enlargement. However, 17 of 32 patients whose tumors were judged by the attending physicians as showing enlargement did not meet the criteria for enlargement set forth in this study, indicating that the extent of enlargement in these cases was within-observer variation. Furthermore, 13 patients were recommended for surgery because of a dorsal tumor location, even though observation had been recommended at the initial diagnosis of PMC. More accurate evaluation of the tumor at the first examination and, if observation is decided, systematic evaluation of tumor size at each follow-up by the attending physician would be a more desirable approach. None of the 109 patients showed carcinoma recurrence or died of carcinoma during postoperative follow-up. It is important to note that, for patients whose tumor is under observation, it would not be too late to perform surgical treatment if there are signs of progression, such as tumor enlargement or novel appearance of lymph node metastasis.

We investigated whether patient backgrounds and clinical features are linked to PMC progression, tumor enlargement, and novel appearance of nodal metastasis. Male gender, multicentricity, and advanced age are known to be conventional prognostic factors of papillary carcinoma [3, 4], but these features did not affect PMC progression during observation. Furthermore, we failed to establish a relationship between carcinoma enlargement and tumor size at diagnosis. It is therefore suggested that all PMC without any unfavorable features can be

candidates for observation regardless of patient background and clinical features. We could not find any evidence that TSH suppression effectively prevents carcinoma progression. However, there were only 27 patients who underwent TSH suppression in this series and further studies are necessary to draw a final conclusion on this issue. The incidence of familial carcinoma in our observation series was 5.0%, which is similar to that in previous reports from Japan with a large series of papillary carcinoma patients undergoing surgical treatment [26, 27]. We showed that the prognosis of familial papillary carcinoma after surgical treatment did not differ from that of non-familial carcinoma [27]. Also in this study, the rate of progression of familial PMC was the same as that of non-familial PMC in the observation group, indicating that immediate surgical treatment is not mandatory for familial PMC patients unless they have any unfavorable features or show progression during observation.

We previously demonstrated that PMC patients having clinically apparent lateral node metastasis (N1b) were more likely to show recurrence [20, 21]. This was confirmed on multivariate analysis in this study, indicating that N1b is an independent prognostic factor for DFS of PMC patients. The organ to which carcinoma most frequently shows recurrence is the lymph node, and recurrence to the compartment that had previously been dissected occurred with an incidence similar to that of recurrence to the compartment that had not previously been dissected. Even though the primary tumor is small, surgeons should carefully perform therapeutic lymph node dissection at first surgery for N1b PMC. Together with N1b, massive extrathyroid extension (pT4) also significantly affects the prognosis of papillary carcinoma [3, 4], but in our series, none of the patients with pT4 had carcinoma recurrence. The number of pT4 patients was small at 25, accounting only for 2.4% of this series, and the range of extension to adjacent organs is very limited for pT4 PMC, which may explain our findings.

In our previous study, we showed that in a subset of PMC patients without clinically apparent node metastasis, recurrence rate to the lymph node in patients who underwent central node dissection only did not differ from that in patients who underwent prophylactic MND [20, 21]. In addition, in this study, we demonstrated that these rates were similar to the rate of novel appearance of lymph node metastasis from PMC in the observation group. Our findings that the incidence of the novel appearance of lymph node metastasis in the observation group is as low as that of recurrence to the nodes in the immediate surgical treatment group, and that none of the patients showed recurrence even though they had undergone surgery after the appearance of nodal metastasis, further support the validity of observation for PMC from the perspective of lymph node metastasis.

In summary, we demonstrated that observation can be a therapeutic option for PMC without unfavorable features regardless of patient background and clinical features. It is not too late to perform surgical treatment after carcinoma shows signs of progression, such as tumor enlargement and/or the appearance of lymph node metastasis.

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