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ORIGINAL

# Observational management of papillary microcarcinoma appearing in the remnant thyroid after hemithyroidectomy

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**Abstract.** Active surveillance for papillary thyroid microcarcinomas (PTMCs) initiated in Japan is becoming adopted worldwide as a management option. However, it remains unclear how to manage newly appearing PTMCs in the remnant thyroid after hemithyroidectomy. We investigated the outcomes of similar observational management (OM) for PTMCs appearing in the remnant thyroid after hemithyroidectomy for papillary thyroid carcinoma (PTC) and benign thyroid nodules. Eighty-three patients were newly diagnosed with PTMC in the remnant thyroid between January 1998 and March 2017. Of these, 42 patients underwent OM with >3 times ultrasound examinations. Their initial diagnoses were PTC (initially malignant group) in 37 patients and benign nodule (initially benign group) in 5 patients. We calculated the tumor volume doubling rate (TV-DR) during OM for each PTMC. The TV-DR (/year) was <–0.1, –0.1–0.1, 0.1–0.5, and >0.5 in 12, 19, 5, and 6 patients, respectively. The TV-DRs in both groups did not statistically differ, but six patients (16%) in the initially malignant group showed moderate growth (TV-DR >0.5/year). They underwent conversion surgery and none of them had further recurrence. The remaining 36 patients retained OM without disease progression. The TV-DR in the initially malignant group was not significantly associated with patients' backgrounds or their initial clinicopathological features. None of the patients in this study showed distant metastases/recurrences or died of thyroid carcinoma. Although a portion of PTMCs appearing after hemithyroidectomy for thyroid malignancy are moderately progressive, OM may be acceptable as a management option for PTMCs appearing in the remnant thyroid after hemithyroidectomy.

*Key words*: Papillary thyroid microcarcinoma, Hemithyroidectomy, Remnant thyroid, Tumor volume doubling rate

**SINCE 1993**, observational management (OM) for T1aN0M0 papillary thyroid carcinoma (PTC), namely low-risk papillary thyroid microcarcinoma (PTMC), has been performed at our institution [1]. Thereafter, it became known as active surveillance (AS) because of its prospective design. The outcomes of patients who underwent AS were excellent; only 8% of the PTMCs enlarged by ≥3 mm, and only 3.8% of these showed newly developed lymph node metastasis at 10-year AS [2]. In addition, none of the patients showed distant metastases or died of thyroid carcinoma during AS and after conversion surgery because of carcinoma progression. These findings strongly suggest that AS is a safe management strategy for PTMCs, and other researchers have also reported similar favorable outcomes in patients with PTMCs [3-8]. Recently, the Japan Association of Endocrine Surgeons published consensus statements for performing AS for PTMCs [9].

In Japan, less-than-total thyroidectomy has often been performed for less advanced PTC confined to the thyroid lobe; the 2015 American Thyroid Association (ATA) guidelines accepted performing hemithyroidectomy for PTC <4 cm without extrathyroidal extension or nodal or distant metastasis [10]. With this procedure for PTC, PTMCs can appear in the remnant thyroid later because of recurrence of the primary lesion or development of a second primary carcinoma [11]. In such cases, many physicians might immediately perform completion thyroidectomy with or without postoperative radioactive iodine ablation. However, completion total thyroidectomy can

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cause various adverse events such as hypoparathyroidism and vocal cord paralysis [12].

Currently there are no guidelines or consensus regarding the management of such cases. For these, three options could be considered; OM without cytology, OM after diagnosis of PTMC on cytology, and surgery after cytology. In our hospital, the management of these cases depends on the physician's discretion. However, as the experience of AS of PTMCs increased, many physicians gradually and naturally began to consider OM for these cases. In this study, we retrospectively investigated the outcomes of performing OM for PTMCs that appeared in the remnant thyroid after hemithyroidectomy for PTC and for benign nodules to evaluate whether this management is appropriate.

## Patients and Methods

### *Patients*

From January 1998 to March 2017, small nodules measuring ≤1 cm appeared in the remnant thyroid of 83 patients who underwent hemithyroidectomy in the past were diagnosed as PTMC on cytology. The initial surgery was for PTC in 65 patients (initially malignant group) and for benign tumors in the remaining 18 (initially benign group) (Fig. 1). None of these patients showed other local and distant recurrences. Of these 83 patients, 52 and 31 underwent initial surgery at Kuma Hospital and in other hospitals, respectively. After physicians' discretion and patients' informed consent were obtained, 23 patients in the initially malignant group and 13 patients in the initially benign group underwent total thyroidectomy within 6 months after the diagnosis, and the remaining 47 patients underwent OM. Of these 47 patients, 5 underwent ultrasound examination two times or less, and were thus excluded from the present study. This study enrolled 42 patients: 37 (30 females and 7 males) from the initially malignant group and 5 (all females) from the initially benign group who underwent OM with three or more ultrasound examinations. During OM, patients underwent periodic ultrasound examinations with measurements of tumor diameters once or twice per year according to AS for conventional PTMCs. Their OM periods ranged from 9.6 to 192.3 months (median: 61 months). The number of ultrasound examinations ranged from 3 to 25 times (median: 5.5 times). The period from the initial surgery to the detection of newly appearing PTMCs ranged from 30 to 444 months (median: 149.2 months). This study was approved by the Ethics Committee of Kuma Hospital (No. 20200709-1).

### *Evaluation of PTMC growth by maximal diameter*

We have traditionally evaluated PTMC growth by measuring the maximal diameter [2]. We regarded PTMC showing size increase in maximal diameter by ≥3 mm as enlargement.

### *Evaluation of PTMC growth by tumor volume-doubling rate (TV-DR)*

Doubling time (DT) is a well-validated method for analyzing and expressing changes over time in serum tumor marker levels and tumor volume [7, 13-15]. However, this has two major limitations. First, if some of the tumors showed a decrease in these values over time, DTs for these tumors were given negative values, which created a serious problem of discontinuity from the positive values [15]. Second, the magnitude of the DT is

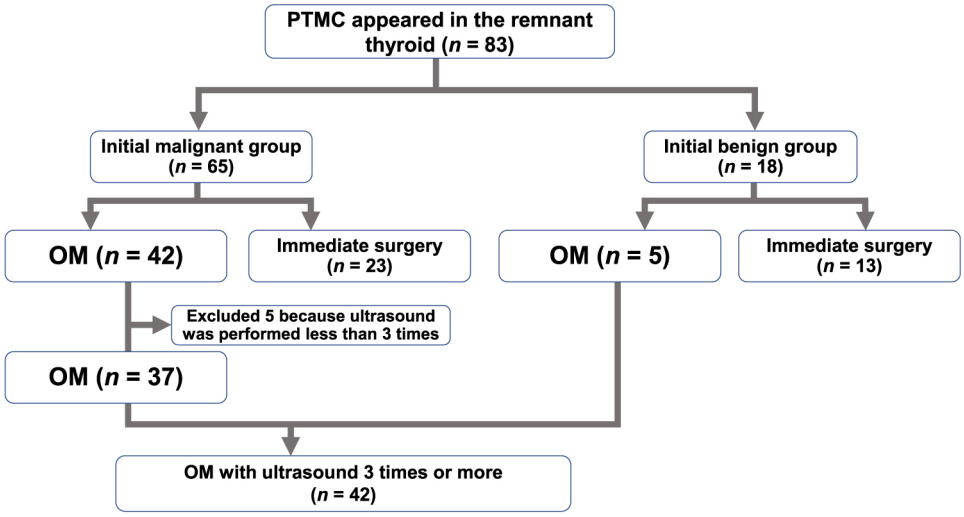


**Fig. 1** A flow chart of the management of PTMCs appearing in the remnant thyroid after hemithyroidectomy. PTMC, papillary thyroid microcarcinoma; AS, active surveillance.

opposite to the growth rate [16]. Taking the inverse of DT, that is, 1/DT, resolves these limitations [15, 16]. We propose calling this index doubling rate (DR) as it indicates the number of doublings per unit time [16].

In the present study, we measured the maximum diameter ($D_1$) and the diameter perpendicular to it ($D_2$). Tumor depth was not reliable in some cases because of ultrasound shadowing. The tumor volume was calculated using the ellipsoid equation ($\pi/6 \times D_1 \times D_2^2$), followed by the calculation of TV-DRs (1/year) of the PTMCs, as described in previous reports [16]. One can easily calculate the TV-DR using the Doubling Time, Doubling Rate & Progression Calculator (https://www.kuma-h.or.jp/english/about/doubling-time-progression-calculator/). Positive TV-DR values indicate an increase in tumor volume over time, and higher values indicate rapid growth. Negative values indicate a shrinkage or decrease in the tumor volume over time. In the present report, a TV-DR of >0.5/year was classified as moderate growth, 0.1/year to 0.5/year as slow growth, –0.1/year to 0.1/year as stable, and <–0.1/year as decreased. We previously called TV-DR of >0.5/year as "rather rapid growth" [15], but after publication, native speakers suggested that "moderate growth" would be more suitable than rather rapid growth. Therefore, in this manuscript, we use "moderate growth" for TV-DR >0.5/year.

### *Statistical analyses*

The Mann-Whitney *U* test and Chi-square test were used to compare the variables, and all statistical analyses were performed using Stat Flex (Artec, Osaka, Japan). Statistical significance was set at $p < 0.05$.

## Results

Of the 83 patients in our series, 47 underwent OM and 36 received immediate surgery. Table 1 shows patients' backgrounds and tumor size at the time of diagnosis for both groups. No significant difference could be detected for patients' age, gender, and tumor size between the two groups.

Table 2 indicates the growth activity of 42 PTMCs based on the change in maximal diameter. Nineteen percent of PTMCs enlarged, while 12% of these shrunk. No significant difference in tumor growth was observed between the initially malignant group and the initially benign group.

We then evaluated tumor growth based on TV-DR, which is more sensitive than the evaluation based on maximal diameter. Fig. 2 shows the TV-DRs of individual PTMCs during AS in the recent study. Of the 42 patients, 6 (16%), 5 (12%), 19 (45%), and 12 patients (29%) were classified as having moderate growth, slow growth, stable, and decreased, respectively, based on their TV-DR values (Table 3). We compared the TV-DR of the 37 PTMCs in the initially malignant group (–1.05/year to 1.84/year, median 0.08/year) with that of the 5 in the initially benign group (–0.46/year to 0.20/year, median –0.02/year), but there was no significant difference between the two groups (Fig. 3). However, evaluation of growth activity based on the four categories showed that 6 (16%) PTMCs in the initial malignant group, but none of those in the initial benign group, were classified as having moderate growth (Table 3, Fig. 3).

**Table 1** Difference in backgrounds and tumor size between patients who underwent OM and immediate surgery

| Variables | No. of patients $N = 83$ | OM $N = 47$ | Immediate surgery $N = 36$ | *p*-values |
|---|---|---|---|---|
| Age (yrs)* | | 50.7 (27–76) | 50.8 (19–77) | 0.48 |
| Gender (Female:Male) | 71:12 | 40:7 | 31:5 | 0.66 |
| Tumor size (mm)* | | 6.2 (3–10) | 6.8 (4–10) | 0.29 |

*: median (ranges)

**Table 2** Growth activity of papillary thyroid microcarcinomas evaluated on change in maximal diameter in the initial malignant group and initial benign group

| Initial Surgery | No. of Patients | Growth activity | | |
|---|---|---|---|---|
| | | +3 mm | –2– +2 mm | –3 mm |
| Malignant | 37 | 7 (19%) | 26 (70%) | 4 (11%) |
| Benign | 5 | 1 (20%) | 3 (60%) | 1 (20%) |
| Total | 42 | 8 (19%) | 29 (69%) | 5 (12%) |

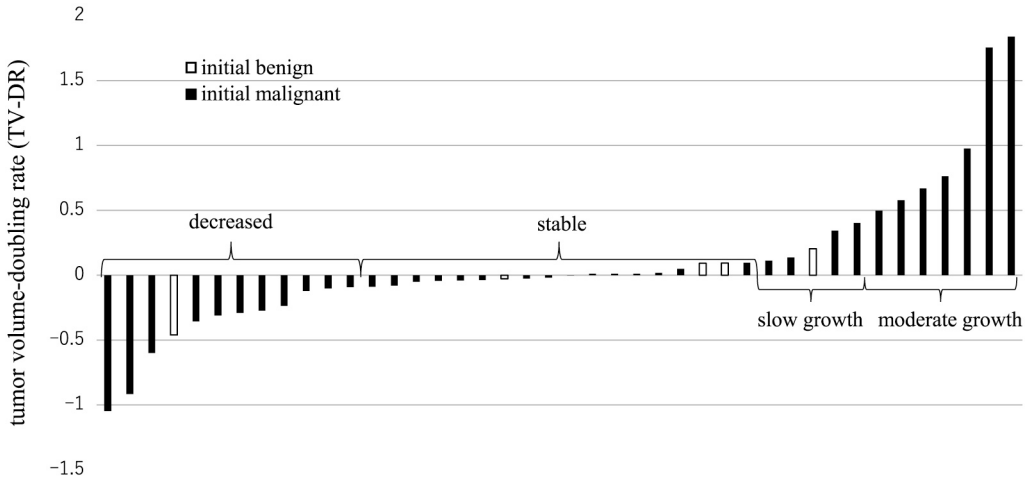


**Fig. 2** Tumor volume-doubling rates (TV-DR) in individual papillary thyroid microcarcinomas during active surveillance. Positive values indicate tumor growth and large values indicate rapid growth. Negative values indicate tumor regression. A TV-DR of >0.5/year was classified as moderate growth, 0.1/year to 0.5/year as slow growth, –0.1/year to 0.1/year as stable, and <0.1/year as decrease.

**Table 3** Growth activity of papillary thyroid microcarcinomas evaluated on tumor volume-doubling rate in the initial malignant group and initial benign group

| Initial Surgery | No. of Patients | Growth activity | | | |
|---|---|---|---|---|---|
| | | Moderate growth | Slow growth | Stable | Decrease |
| Malignant | 37 | 6 (16%) | 4 (11%) | 16 (43%) | 11 (30%) |
| Benign | 5 | 0 (0%) | 1 (20%) | 3 (60%) | 1 (20%) |
| Total | 42 | 6 (14%) | 5 (12%) | 19 (45%) | 12 (29%) |

A tumor volume-doubling rate of >0.5/year was classified as moderate growth, 0.1/year to 0.5/year as slow growth, –0.1/year to 0.1/year as stable, and <0.1/year as decrease.

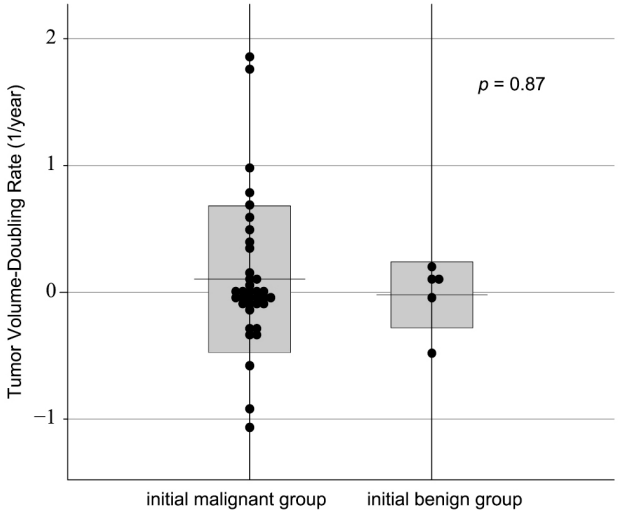


**Fig. 3** Tumor volume-doubling rates of papillary thyroid microcarcinomas in the initial malignant group and initial benign group.

Next, we performed subset analyses of 37 patients in the initially malignant group. The initial surgeries for 19 patients were performed at Kuma Hospital, while the remaining 18 had their initial surgery at other hospitals. Based on the TV-DR, we combined moderate growth and slow growth as the growing group ($n$ = 10), and stable and decreased as the non-growing group ($n$ = 27). Nineteen patients who underwent initial surgery at Kuma Hospital had tumor sizes ranging from 5 mm to 31 mm (median, 19 mm), and five (26%) patients had few small node metastases (cN) detectable with imaging studies. However, none of the patients were positive for high-risk features, such as significant extrathyroid extension, extranodal tumor extension, or large cN (>3 cm) [17-19], at the initial surgery. The clinicopathological features of the 18 patients who were initially treated in other hospitals are unknown. The TV-DR was not significantly related to patient backgrounds such as age and gender, or clinicopathological features of initial surgery such as tumor size, cN status, multiplicity (evaluated on ultrasound), and time to appearance of novel PTMC (Table 4).

**Table 4** Backgrounds and clinicopathological features in the growing group and non-growing group based on tumor volume-doubling rate

| Backgrounds | No. of patients $N = 37$ | Growing Group $N = 10$ | Non-growing Group $N = 27$ | $p$-values |
|---|---|---|---|---|
| Age (yrs)* | | 56.9 (35–75) | 51.6 (35–76) | 0.28 |
| Female:Male | 31:6 | 9:1 | 22:5 | 0.24 |
| Clinicopathological features at initial surgery** | $N = 19$ | $N = 7$ | $N = 12$ | |
| Tumor size (mm)* | | 19 (5–31) | 26 (7–30) | 0.68 |
| cN0 | 14 (74%) | 6 (87%) | 8 (66%) | |
| cN1a | 2 (10%) | 0 (0%) | 2 (17%) | 0.31 |
| cN1b | 3 (16%) | 1 (13%) | 2 (17%) | |
| Presence of multiple lesions | | 2 (29%) | 3 (25%) | 0.24 |
| Time to appearance of PTMC (month)* | | 103 (45–444) | 138.5 (30–332) | 0.23 |

*: median (ranges), **: 18 patients who underwent initial surgery at other hospitals were excluded.

To date, 6 patients having PTMCs with moderate growth underwent conversion surgery 7.7–91.8 months after the initiation of OM; none of these patients showed further recurrence. The remaining 36 remained under OM with no signs of progression such as significant tumor enlargement or a novel appearance of lymph node metastasis. In addition, in the present series, none of the patients showed distant metastases/recurrences, or died of thyroid carcinoma during OM and after conversion surgery.

Of the 36 patients who underwent immediate surgery, 2 (6%), 2 (6%), and 7 patients (19%) suffered postoperative bleeding requiring re-operation, transient recurrent laryngeal nerve paralysis, and transient hypoparathyroidism, respectively. None of these patients had persistent recurrent laryngeal nerve paralysis or persistent hypoparathyroidism.

## Discussion

In this study, we retrospectively investigated whether OM is acceptable as a management strategy for newly arisen PTMC in the remnant thyroid after hemithyroidectomy. The number of enrolled patients is too small to draw any definite conclusions, but we currently showed that 16% of PTMCs in the initial malignant group showed moderate growth and underwent conversion surgery. In contrast, none of the patients in the initially benign group were classified as moderate growth. Miyauchi *et al.* showed that only 5 (3%) of 169 patients with PTMC showed moderate growth with a TV-DR of >0.5/year during AS for a median period of 10.1 years [16]. Compared with their study, the incidence of moderate growth in the initially malignant group in the present study was higher.

In the initially malignant group, none of the 19 patients who underwent initial surgery in our hospital had high-risk features of PTC such as significant extrathyroid extension, extranodal extension, and cN >3 cm [17-19]. However, this group included PTCs with tumor size of >1 cm and/or small cN, which should be more aggressive than low-risk PTMCs. Furthermore, the clinicopathological features at initial surgery are unknown for patients treated in other hospitals. If newly appearing PTMCs in the remnant thyroid are recurrences of primary lesions with aggressive features, their growth activity might be higher than that of conventional PTMCs. This might explain, at least in part, the higher incidence of cases showing moderate growth in PTMCs in the initial malignant group than in the series of Miyauchi *et al.* [16].

As shown in Table 4, we could not find any significant difference in patient backgrounds and clinicopathological features at initial surgery between the growing group and the non-growing group. We previously showed that PTMC in young patients are more likely to grow than in elderly patients [2], but patient age was not significantly related to tumor growth in the present series. This may be because of the small number of patients in our series, or because the present series included recurrences of PTC with more aggressive characteristics than low-risk PTMC.

In our series of initially malignant groups, as shown in Table 3, 11%, 43%, and 30% were classified as slow growth, stable, and decreased in size, respectively. All these patients remained in the OM without further

disease progression. Conversion surgery was performed in six patients with PTMCs showing moderate growth, and none of these patients showed further recurrence. Besides, none of the patients in our series showed distant metastases/recurrences or died of thyroid carcinoma under close observation. Therefore, OM might be one of the management options for PTMCs newly appearing in the remnant thyroid after initial surgery for PTC; although the incidence of progressing tumors could be slightly higher than that in conventional PTMCs. Conversion surgery can be performed in patients with enlarged tumors to produce favorable outcomes in the patients.

This study has some limitations. First, this was a retrospective study, and the management of PTMCs in the remnant thyroid was not decided in advance. Second, the number of patients enrolled in this study was small, which may explain the lack of a relationship between growth activity and various patient backgrounds and clinicopathological features. Third, since we do not always perform cytological examination for small nodules suspected of PTMC in the remnant thyroid, there may be some biases by making analyses only for patients who underwent cytological examination. Fourth, whether patients undergo OM (47 patients) or immediate surgery (36 patients) has been decided by various factors, including patients' preferences, backgrounds, and physicians' recommendation, indicating that there may also be some biases between the two groups. However, the current report is the first and the largest to describe the management of this rare condition. Toumi *et al.* showed that the proportion of hemithyroidectomy in thyroid carcinoma increased from 17% in 2015 to 28% by the end of 2018 after the release of the current ATA guidelines accepting hemithyroidectomy for less advanced PTC [20]. Therefore, the incidence of the condition described in this report is expected to increase worldwide.

In summary, we showed our thus far favorable outcomes of patients who underwent OM with periodic ultrasound examination for PTMCs appearing in the remnant thyroid after hemithyroidectomy for PTC. However, additional genetic testing and a long-term prognostic evaluation for larger number of patients are necessary to conclude whether OM for these PTMCs is acceptable as a management strategy.

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## Disclosure

No competing financial interests exist.

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