Favorable outcomes of papillary thyroid microcarcinoma concurrent with Graves’ disease after radioactive iodine therapy

Eijun Nishihara*, Yasuhiro Ito*, Takumi Kudo, Mitsuru Ito, Shuji Fukata, Mitsushige Nishikawa, Takashi Akamizu and Akira Miyauchi

Kuma Hospital, Center for Excellence in Thyroid Care, Kobe, Japan

Abstract. Graves’ disease (GD) may coexist with papillary thyroid microcarcinoma (PTMC). The main purpose of this study was to evaluate whether treatment with radioactive iodine (RAI) may cause acute exacerbation of PTMC concurrent with GD or not. From the medical records of 10,257 GD patients who underwent RAI therapy between 2000–2017, 12 subjects with concurrent PTMC were retrieved. Further, 49 patients with concurrent GD and PTMC who underwent no RAI administration throughout their clinical course were enrolled as controls. Size of the PTMC nodules was evaluated based on maximal diameter and tumor volume-doubling rate (TV-DR). Among the 12 subjects who underwent RAI therapy (median dose, 13 mCi), 2 showed tumors >10 mm in maximal diameter with slow growth for more than 10 years, while the other 10 showed tumors with maximal diameter ≤10 mm. No subject showed any clinical findings of nodal or distant metastasis during the follow-up periods (0.4–11.5 years) before surgery or during active surveillance. No significant differences were observed in the TV-DR values (median, 0.044/year; range, –0.81–1.40) between the study subjects and controls (median, 0.025/year; range, –0.70–1.29; \( p = 0.69 \)). When comparing the TV-DR before and after RAI administration in 3 individuals in particular, in whom PTMC were cytologically confirmed before RAI administration and whose prospective follow-up data were available, tumor progression was observed to be stable or decreased after RAI administration. There were no acute exacerbations or unfavorable outcomes of concurrent PTMC and GD after low-dose RAI administration.

Key words: Papillary thyroid microcarcinoma, Graves’ disease, Radioactive iodine therapy, Active surveillance, Tumor volume-doubling rate

GRAVES’ DISEASE (GD) is most prevalent among patients with hyperthyroidism in iodine-rich areas. Three treatment options, namely, anti-thyroid drugs (ATDs), radioactive iodine (RAI) therapy, and surgery, have been adopted for GD on a case-by-case basis. GD often coexists with thyroid nodules, including carcinoma. An in vitro study reported that IgG isolated from the serum of GD patients stimulated the growth of thyroid cancer cells [1]. According to a review by Stocker et al. [2], thyroid carcinoma coexists with GD in ≤2% cases, and immediate surgery after cytological diagnosis is generally recommended in such cases.

Papillary thyroid microcarcinoma (PTMC) is characterized as papillary thyroid carcinomas (PTCs) measuring ≤10 mm in diameter. Kituchi et al. showed an excellent prognosis of PTMCs when concurrent with GD, with a 20-year disease-free survival rate of 99% if the tumors were surgically removed [3]. However, active surveillance of PTMCs has recently been widely adopted for patients with concurrent GD without high-risk features such as clinical lymph node and/or distant metastases and significant extrathyroid extension [4-7]. Microcarcinomas account for 68% of GD cases with thyroid carcinoma [6], and the prevalence of microcarcinomas in patients with GD is significantly higher than that in euthyroid controls [8, 9]. Achieving remission of GD by ATDs is difficult in the presence of PTMC; however, whether surgery should be mandatory, or whether RAI therapy is effective for such cases, remains an open question.

The American Thyroid Association (ATA) guidelines for the diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis recommend cytological
evaluation of thyroid nodules >10–15 mm before initiating RAI therapy; if the nodule is suspected or diagnosed to be malignant, the guidelines recommend surgery after normalization of thyroid function using ATDs [10]. However, the guidelines do not comment on the evaluation of thyroid nodules sized ≤10 mm, which include PTMCs. Indeed, the ATA guidelines for adult patients with thyroid nodules and differentiated thyroid cancer suggest the indication of cytological examination to be nodules >10 mm if none of the malignant findings such as lymph node and/or distant metastasis, invasion to the surrounding organs, and recurrent laryngeal nerve paralysis were detected on imaging and fiberscope studies [11]. The 2018 European Thyroid Association (ETA) guidelines for the management of Graves’ hyperthyroidism recommend thyroidectomy for patients with suspected malignant nodules [12].

In this study, we retrospectively studied the outcomes of concurrent PTMC and GD, which was incidentally or purposely treated with RAI, to investigate whether RAI therapy may cause acute exacerbation of PTMC or not.

Materials and Methods

Subjects
The patient sample was selected from GD patients treated at Kuma Hospital. Among them, 10,257 patients underwent RAI therapy between 2000 and 2017, while 309 were diagnosed with concurrent PTMC during the same period, through ultrasound detection of one or more nodules sized ≤10 mm and subsequent cytological confirmation. Fig. 1 illustrates the management approach adopted throughout the clinical course of such patients, alongside the participant selection process. For this study, 12 subjects who fulfilled the following 3 conditions were enrolled: 1) ultrasound detection of one or more nodules sized ≤10 mm within 6 months before RAI therapy, 2) periodic follow-up ultrasound evaluation of nodules (at least twice) after RAI therapy, and 3) cytological diagnosis of the nodules as PTC before or after RAI therapy. Among these 12 patients (Table 1), one was male and the remaining were female, with age ranging between 39 and 74 years (median, 46 years). PTMCs in 4 patients were cytologically diagnosed before RAI therapy initiation, whereas those in 8 patients, although detected by ultrasound before RAI therapy, were only cytologically diagnosed after therapy initiation. PTMCs in 12 subjects showed clinically low-risk features (T1aN0M0). The median total thyroid volume was 35 mL (range, 16–97 mL), and the median RAI dose was 13 mCi (range, 4–13 mCi).

We consecutively enrolled 49 GD patients with cytologically confirmed PTMCs who initiated thiamazole treatment between 2006 and 2017 as controls. No controls underwent RAI therapy throughout their clinical course, and the nodules in these patients were also followed-up periodically (at least 3 times) by ultrasound. PTMCs in 49 controls showed clinically low-risk features at diagnosis. Among the controls, two were male and the remaining were female, with age ranging between 27 and 74 years (median, 52 years). During the follow-up (median, 6.0 years; range, 0.5–12.3 years), 12

Fig. 1 Study flow chart of the treatment approach for patients with concurrent Graves’ disease and papillary thyroid microcarcinoma.

*: 13 patients were overlapped in both groups
GD, Graves’ disease; PTMC, papillary thyroid microcarcinoma; RAI, radioactive iodine
patients underwent surgery, 14 continued ATD treatment, and 23 discontinued medication due to remission of Graves’ hyperthyroidism.

Graves’ disease was diagnosed based on the presence of hyperthyroidism, positive thyrotropin receptor antibodies (TRAb), and increased radioiodine uptake by the thyroid. The study protocol was approved by the Ethics Committee of Kuma Hospital (approval number: 20170309-3). Informed consent was obtained from each patient prior to the initiation of this study.

Maximal diameter and tumor volume-doubling rate

To evaluate the progression of PTMC, maximal diameter and tumor volume-doubling rate (TV-DR) determined via serial ultrasound were used as described previously [13, 14]. Briefly, tumor volume (V) was calculated using the ellipsoid equation (π/6 × D_1 × D_2 × D_3) or (π/2 × D_1 × D_2^2), with D_1 being the maximum diameter, D_2 the diameter perpendicular to the maximum diameter, and D_3 the tumor depth, which is often unreliable due to ultrasound shadowing. The coefficient of variance (CV) in tumor volume calculated using 3-dimensional measurement was 9.6% at Kuma Hospital [15]. TV-DR was measured as α/log2, with time (T) set as the time interval between presentation and measurement, and α calculated based on the following formula [13].

\[
\alpha = \left( \frac{\sum T_i \times \log(V_i) - \sum T_i \times \sum \log(V_j)}{\sum T_i^2 - \left(\sum T_i\right)^2} \right)
\]

TV-DR is the inverse of tumor doubling time, and is used to balance out the positive and negative values; it indicates the number of doublings occurring in unit time (e.g., a year).

Change in nodule size was considered as enlargement or shrinkage when the maximal diameter increased or decreased by ≥3 mm, respectively, while others would be classified as stable. TV-DR was classified into 4 categories: rapid growth (>0.5), slow growth (0.1–0.5), stable (–0.1–0.1), and decrease (<–0.1).

Statistical analysis

Differences between age, follow-up period, and categorized maximal diameter and TV-DR values in PTMC subjects and controls were evaluated using the Mann-Whitney U test. Differences were considered significant when \( p < 0.05 \). Statistical analyses were performed using StatFlex version 6.0 (Artech Co. Ltd., Japan).

Results

Table 1 shows the detailed backgrounds of the 12 subjects included in our study. Five patients (Nos. 1–5) underwent surgery after RAI therapy either immediately after cytological diagnosis, or as a conversion surgery due to tumor enlargement. The histopathological findings of these 5 patients indicated well-differentiated papillary thyroid carcinomas. Only 1 patient (No. 5) pathologically showed central node metastasis, while the others showed no clinical findings of nodal or distant metastasis during their follow-ups after RAI therapy.
(median follow-up duration, 5.0 years; range, 0.4–11.5 years). The remaining 7 patients (Nos. 6–12) underwent active surveillance after RAI therapy for 2.2–11.3 years. Serum TSH levels in the 12 subjects before surgery or during active surveillance were maintained around the lower limit of the normal range with levothyroxine (LT4) (Nos. 1, 2, 4, 6, 7, 8, and 12), thiamazole (Nos. 5 and 11), or no medication (Nos. 3, 9, and 10). Complications with heart diseases such as chronic heart failure and atrial fibrillation were observed in 3 patients (Nos. 4, 9, and 11). Past history showed severe side effects to ATDs in 3 patients (Nos. 1, 7, and 8), and relapse of GD in 2 patients (Nos. 10 and 12). The ages and follow-up periods were not significantly different between the subjects and controls ($p = 0.94$ and $p = 0.68$, respectively).

During follow-up after RAI therapy (Table 2), the maximal diameter of tumors was observed to be increasing in 2 patients (Nos. 1 and 2), stable in nine (Nos. 3–11), and decreasing in one (No. 12). Among the controls, the maximal diameter of tumors was increasing in 4 patients, stable in 43, and decreasing in two. The proportion of individuals with increasing, stable, and decreasing maximal diameters of tumors was not significantly different between the subject and control groups ($p = 0.71$). The median TV-DR was 0.044/year (range, –0.81–1.40); the TV-DR showed rapid growth in 1 patient (No. 4), slow growth in four (Nos. 1, 2, 5, and 7), was stable in four (Nos. 3, 6, 8, and 9), and decreased in three (Nos. 10, 11, and 12). In controls, TV-DR values showed a median of 0.025/year (range, –0.70–1.29), and showed rapid growth in 4 patients, slow growth in five, was stable in 33, and decreased in seven. Four controls whose tumors showed rapid growth underwent conversion surgery during their clinical courses (Fig. 1). TV-DR values showed no significant differences between the subject and control groups ($p = 0.69$). Data for TV-DR assessment before RAI therapy (at least 3 ultrasound measurements of tumor size) were available for only 3 patients (Nos. 9, 10, and 12), and the tumor size in one of them (No. 12) showed an apparent decrease after RAI administration.

**Discussion**

This is the first study demonstrating the outcomes of RAI therapy in cases of concurrent PTMC and GD. Among the 12 PTMC patients, two showed tumors >10 mm in maximal diameter with slow growth for more than 10 years, while the other 10 patients showed tumors sized ≤10 mm. No patient showed any clinical findings of nodal or distant metastasis before surgery or during active surveillance. Overall, there were no clinical findings concerning acute exacerbation of PTMC after low-dose RAI administration (≤13 mCi) in the present study.

For further precise evaluation of changes in tumor size, we adopted the TV-DR measurement, a kinetic analysis using three-dimensional measurements of tumors. Miyauchi et al. recently evaluated PTMC progression during active surveillance via TV-DR divided into 4 categories [13], which have been applied in our

| Patient No. | Follow-up period after RAI therapy (year) | Maximal diameter of tumor | TV-DR after RAI therapy (/year) | TV-DR before RAI therapy (/year) |
|-------------|------------------------------------------|---------------------------|---------------------------------|----------------------------------|
|             | Before RAI therapy (mm) | After follow-up (mm) |                                 |                                 |
| 1           | 11.1          | 8                        | 16                              | 0.22 [NA]                       |
| 2           | 11.5          | 7                        | 18                              | 0.32 [NA]                       |
| 3           | 0.4           | 6                        | 6                               | –0.068 [NA]                     |
| 4           | 1.4           | 7                        | 9                               | 1.4 [NA]                        |
| 5           | 1.2           | 5                        | 5                               | 0.29 [NA]                       |
| 6           | 7.3           | 8                        | 7                               | 0.005 [NA]                      |
| 7           | 6.1           | 7                        | 9                               | 0.11 [NA]                       |
| 8           | 11.3          | 10                       | 9                               | 0.031 [NA]                      |
| 9           | 6.3           | 5                        | 5                               | 0.058 [0.042]                   |
| 10          | 3.8           | 6                        | 4                               | –0.81 [–0.34]                   |
| 11          | 2.2           | 7                        | 6                               | –0.8 [NA]                       |
| 12          | 3.1           | 10                       | 7                               | –0.66 [0.38]                    |

TV-DR, tumor volume-doubling rate; NA, not available
study. In both the subject and control groups, rapid growth was detected only in 8% of patients, and TV-DR values showed no significant differences (p = 0.69). Based on the results of both maximal diameter and TV-DR values, low-dose RAI administration seemed to confer no progressive growth of PTMCs. Minor discrepancies in tumor growth observed between maximal diameter and TV-DR values in 5 subjects (Nos. 4, 5, 7, 10, and 11). These subjects showed the shorter observation periods (median, 2.2 years; range, 1.2–6.1 years) than the other 7 subjects (median, 7.3 years; range, 0.4–11.5 years). This suggests that evaluation by TV-DR is very sensitive for microcarcinoma because the changes of ≤2 mm in each direction may lead to meaningful changes of the tumor growth, especially under small number of measurements due to short observation periods which may be subject to observer variability [7]. The CV for each ultrasonographer at Kuma Hospital was approximately 20% [15].

In this study, 8 of 12 subjects (67%) previously or currently presented with one of the following: severe side effects to ATDs, GD relapse, and heart diseases. Since the malignant potential of PTMCs in GD patients has been reported to be almost similar to that in patients without GD [9, 16], surgery is not highly recommended, especially for those with a high risk of complications, such as heart diseases, diabetes mellitus, and renal failure. In addition, patients with severe side effects to ATDs or GD relapse after ATD withdrawal should discontinue ATD treatment and consider ablative therapy. These situations are likely to be applicable to GD patients with PTMCs, leading to the initiation of RAI therapy incidentally or purposely. Based on our data, RAI therapy, when accompanied by periodic ultrasound examination and the maintenance of low normal TSH levels thereafter, may be suitable for GD patients with PTMC who show some disadvantages with ATD treatment and surgery.

Our study had several limitations. First, a selection bias for subjects may have been present because of the retrospective nature of the analysis. Surgery was selected as ablative therapy 9 times as many than RAI therapy during the clinical course of GD patients with concomitant PTMCs (Fig. 1). PTMCs with clinical lymph node metastases and attaching to the trachea were indicated for immediate surgery, which were only 7.4 % (23/309). More than 40% of patients with the remaining low-risk PTMCs underwent surgery (Fig. 1). Furthermore, a large proportion of PTMCs (8/12, 67%) was confirmed by fine needle aspiration cytology after RAI administration. However, these cases with low-risk PTMCs showed no clinical aggravation even though the main reasons for the cytological analyses were tumor enlargement during surveillance and reexamination due to insufficient specimens for previous evaluations. Second, a relatively low number of subjects were included in the analysis with varying follow-up periods (0.4–11.5 years). However, the additional comparison of TV-DR before and after RAI administration in 3 individuals (Nos. 9, 10, and 12), in whom PTMC was cytologically confirmed before RAI initiation and whose data were available for prospective follow-up, showed that tumor progression was either stable or decreased after RAI administration.

Collectively, our retrospective study showed no acute exacerbations or unfavorable outcomes after RAI administration in patients with concurrent PTMC and GD. Further continuous follow-up is indispensable for available subjects and controls in this study. Moreover, prospective analyses with larger cohorts and longer surveillance periods are warranted to provide more precise information concerning the outcomes.

Acknowledgements

We thank Ms. Izumi Otsuka for extracting data from the electronic medical chart system.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

References

1. Filetti S, Belfiore A, Amir SM, Daniels GH, Ippolito O, et al. (1988) The role of thyroid-stimulating antibodies of Graves’ disease in differentiated thyroid cancer. N Engl J Med 318: 753–759.

2. Stocker DJ, Foster SS, Solomon BL, Shriver CD, Burch HB (2002) Thyroid cancer yield in patients with Graves’ disease selected for surgery on the basis of cold scintiscan defects. Thyroid 12: 305–311.

3. Kikuchi S, Noguchi S, Yamashita H, Uchino S, Kawamoto H (2006) Prognosis of small thyroid cancer in patients with Graves’ disease. Br J Surg 93: 434–439.

4. Miyauchi A, Ito Y (2019) Conservative surveillance management of low-risk papillary thyroid microcarcinoma. Endocrinol Metab Clin North Am 48: 215–226.

5. Sugitani I, Ito Y, Miyauchi A, Imai T, Suzuki S (2019) Active surveillance versus immediate surgery: questionnaire survey on the current treatment strategy for adult patients with low-risk papillary thyroid microcarcinoma in Japan. Thyroid 29: 1563–1571.

6. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi
K, et al. (2014) Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid* 24: 27–34.

7. Sugitani I, Ito Y, Takeuchi D, Nakayama H, Masaki C, et al. (2020) Indications and strategy for active surveillance of adult low-risk papillary thyroid microcarcinoma: consensus statements from the Japan Association of Endocrine Surgery task force on management for papillary thyroid microcarcinoma. *Thyroid (in press)*

8. Kasuga Y, Sugenoya A, Kobayashi S, Masuda H, Iida F (1993) The outcome of patients with thyroid carcinoma and Graves’ disease. *Surg Today* 23: 9–12.

9. Hales IB, McElduff A, Crummer P, Clifton-Bligh P, Delbridge L, et al. (1992) Does Graves’ disease or thyrotoxicosis affect the prognosis of thyroid cancer. *J Clin Endocrinol Metab* 75: 886–889.

10. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, et al. (2016) 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid* 26: 1343–1421.

11. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, et al. (2016) 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 26: 1–133.

12. Kahaly GJ, Bartalena L, Hegedus L, Leenhardt L, Poppe K, et al. (2018) 2018 European Thyroid Association guideline for the management of Graves’ hyperthyroidism. *Eur Thyroid J* 7: 167–186.

13. Miyauchi A, Kudo T, Ito Y, Oda H, Yamamoto M, et al. (2019) Natural history of papillary thyroid microcarcinoma: kinetic analyses on tumor volume during active surveillance and before presentation. *Surgery* 165: 25–30.

14. Ito Y, Miyauchi A, Kudo T, Higashiyama T, Masuoka H, et al. (2019) Kinetic analysis of growth activity in enlarging papillary thyroid microcarcinomas. *Thyroid* 29: 1765–1773.

15. Nakamura H, Hirokawa M, Ota H, Kihara M, Miya A, et al. (2015) Is an increase in thyroid nodule volume a risk factor for malignancy? *Thyroid* 25: 804–811.

16. Kim WB, Han SM, Kim TY, Nam-Goong IS, Gong G, et al. (2004) Ultrasonographic screening for detection of thyroid cancer in patients with Graves’ disease. *Clin Endocrinol (Oxf)* 60: 719–725.