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Long-Term Follow-Up of the Therapeutic Outcomes for Papillary Thyroid Carcinoma With Distant Metastasis

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Abstract: Papillary thyroid carcinoma (PTC) patients with distant metastasis (DM) have variable clinical courses and therapeutic outcomes. Survival time after diagnosis of DM may be several months to years. Long-term follow-up is necessary to determine prognostic factors for survival in PTC with DM. The purpose of this study was to investigate the clinical features and therapeutic outcomes of PTC with DM after 10 years of follow-up. The study population consisted of 70 patients who underwent initial thyroidectomy before 2004 and had DM beyond the locoregional neck area. Of these 70 patients, 40 patients were diagnosed with DM before or within 9 months after initial thyroidectomy in first radioactive iodide (¹³¹I) whole-body scintigraphy (group A), and 30 patients were diagnosed with DM during the follow-up period (group B). Patients with DM underwent 3.7 to 7.4 GBq ¹³¹I therapy every 6 to 12 months. After a mean follow-up period of 10.1 ± 0.9 years, the disease-specific mortality and remission rates were 70.0% (49/70) and 10% (7/70), respectively. The survival rates for patients in groups A and B were 72.5% and 96.7% at 1 year, 47.5% and 90.0% at 5 years, 40.0% and 70.0% at 10 years, 36.4% and 41.1% at 15 years, and 35.0% and 8.0% at 20 years, respectively. The percentage of male and older patients and patients with larger tumor size was higher in the mortality group than in the survival group, whereas the percentage of patients with ¹³¹I avid metastatic lesions (first DM) was lower in the mortality group. The percentage of patients with secondary primary cancers was higher in group B than in group A. In the multiple regression analysis, age and male gender were independently associated with disease-specific mortality. In conclusion, after a mean follow-up of 10.1 years, the disease-specific mortality rate for PTC with DM was 70.0%. Older patients and male PTC patients with DM need more aggressive treatment. The timing of DM diagnosis did not influence disease-specific mortality.

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Abbreviations: ¹³¹I = radioactive iodide, CT = computed tomography, DM = distant metastasis, MRI = magnetic resonance imaging, PET = fluoro-18-deoxyglucose positron emission

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tomography, PTC = papillary thyroid carcinoma, Tg = thyroglobulin, TNM = tumor node metastasis, TSH = thyroid stimulating hormone, WBS = whole-body scintigraphy.

INTRODUCTION

Distant metastasis (DM) of papillary thyroid carcinoma (PTC) may occur at the time of initial thyroidectomy or during follow-up.^{1,2} The lungs and bone are the most common sites for DM from PTC. Patients may be diagnosed before thyroidectomy, immediately after thyroidectomy, or years after thyroidectomy. Although PTC generally carries an excellent prognosis, the presence of DM may affect therapeutic outcomes.^{3,4} In previous studies, the 10-year cause-specific survival of PTC with DM has been reported to be 50% to 75%.^{3,5} Aggressive histological patterns and bone, brain, and multiorgan metastases are associated with early mortality (within 10 years) after DM diagnosis.⁶ Most PTC patients with DM undergo repeated radioactive iodide (¹³¹I) therapy to control distant metastatic spread. We conducted a retrospective study to compare the clinical features of PTC patients diagnosed with DM at initial thyroidectomy and during follow-up. The therapeutic outcomes of PTC with DM after a minimum of 10 years of follow-up and risk factors associated with mortality outcomes were also investigated.

SUBJECTS AND METHODS

Between 1977 and 2013, 3495 patients with thyroid cancer, including 2798 PTC patients (80.1%), underwent regular follow-up care at Chang Gung Medical Center in Linkou, Taiwan. Among the 2798 PTC patients, 1882 patients with tumors >1 cm in size received total or near-total thyroidectomy with or without lymph node dissection (Figure 1). To investigate the long-term therapeutic outcomes of PTC with DM, 909 patients who had undergone their first thyroidectomy before 2004 were selected (Figure 1). This study was approved by the Chang Gung Medical Foundation Institutional Review Board, and the informed consent requirement was waived because of the retrospective nature of the study.

Of the 909 selected PTC patients, 70 (7.7%) patients had DM beyond the locoregional neck area. Of these 70 patients, 40 patients were diagnosed with DM before and within 9 months after initial thyroidectomy in first ¹³¹I whole-body scintigraphy (WBS) (group A), and 30 patients were diagnosed with DM during the follow-up period (group B). All patients were staged using the *Union for International Cancer Control Tumor-Node-Metastasis (TNM) Criteria* (6th ed.).⁷ All thyroid carcinoma tissues were pathologically classified according to the World Health Organization criteria.⁸ Of the 70 PTC patients with DM, 48 patients were classical PTC, 13 patients were follicular variant of PTC, and 9 patients were aggressive variants of PTC (tall cell variant [n = 5]; PTC with poorly differentiated component [n = 4]). DM diagnosis was pathologically verified by biopsy in 11 patients (bone [n = 7], lung [n = 2], chest wall [n = 1], brain [n = 1]), including 8 patients in group A.

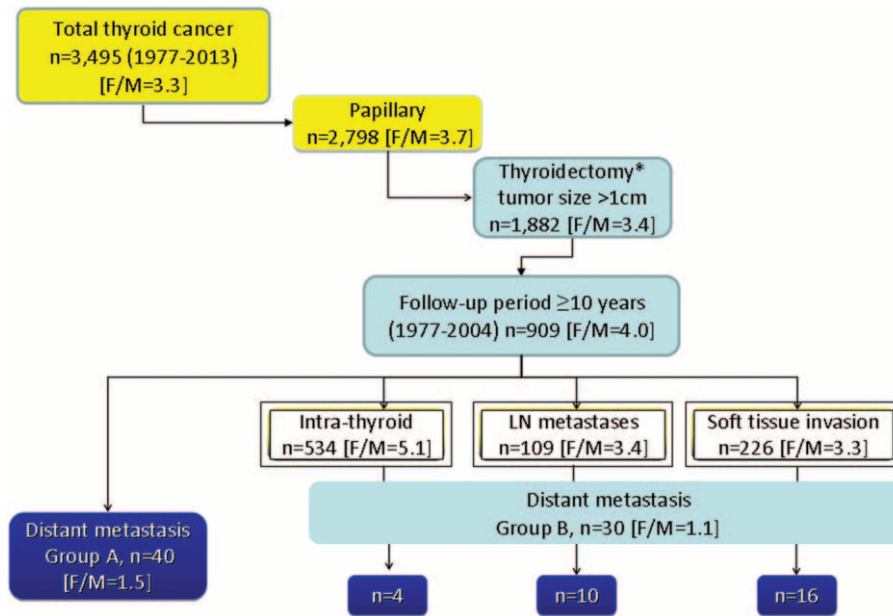


FIGURE 1. Papillary thyroid cancer patients with distant metastasis and long-term follow-up were selected from 3495 patients. Forty patients were diagnosed with distant metastasis before or within 9 months after initial thyroidectomy and ^{131}I whole-body scintigraphy (group A), and 30 patients were diagnosed with distant metastasis during the follow-up period (group B). *Patients who underwent total or complete thyroidectomy with or without limited lymph node dissection.

Depending on the clinical indications, noninvasive examinations included chest radiography, computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy, ^{201}Tl scintigraphy, and fluoro-18-deoxyglucose positron emission tomography (PET). DM was diagnosed by one or more of the following methods: ^{131}I WBS, X-ray, biopsy, CT, MRI, bone scintigraphy, ^{201}Tl scintigraphy, and PET. Multi-organ metastasis was defined as DM in 2 or more organs.

In our center, patients with histologically proven locoregional neck recurrence or PTC patients with DM were advised to undergo thyroid remnant ablation with ^{131}I 4 to 6 weeks after thyroidectomy. One week after 1.1 to 3.7 GBq (30–100 mCi) ^{131}I administration, whole-body images were obtained by continuous mode scanning at a speed of 5 cm/min. In addition, a pinhole collimator with a 4-mm aperture was placed 7 cm above the neck, and thyroid scintigraphy was performed for a total of 50,000 counts or 30 min. After remnant ablation, thyroxine treatment was started to maintain the patients in subclinical hyper- or euthyroidism. For patients with DM identified by ^{131}I uptake extending beyond the thyroid bed, higher therapeutic doses of 3.7 to 7.4 GBq (100–200 mCi) ^{131}I were administered 6 to 12 months later; a therapeutic scan was performed 2 weeks after ^{131}I administration. In Taiwan, patients receiving an ^{131}I dose exceeding 1.1 GBq must be isolated by admission. Radioactive avidity of the lesions was determined in the first positive whole-body scan. External radiotherapy was performed in 29 patients for symptomatic relief of bone metastases or locoregional neck residual and recurrent PTC.

During the follow-up period, thyroglobulin (Tg), thyroid stimulating hormone (TSH), and anti-Tg antibody were tested every 6 months. For patients without DM, a repeat diagnostic scan was performed 6 to 12 months after remnant ablation. An immunoradiometric assay kit (CIS Bio International, Gif Sur Yvette, France) was used for serum Tg determination. Anti-Tg antibody was measured by a competitive radioimmunoassay

(Biocode, Liege, Belgium). The analytical sensitivity was 6 IU/mL; functional sensitivity was measured with the precision of a maximum 20% interassay variance, and the value was <15 IU/mL.

A thyroid cancer database was established in our center in 1995, and data are updated periodically. The database includes demographic information, thyroid histopathology, and cytopathology from other tissues and secondary primary cancers during follow-up of patients with thyroid cancer. ^{131}I therapeutic and diagnostic scanning, ^{131}I avidity of the first DM, noninvasive imaging studies, and laboratory data are also included. In addition, therapeutic outcome, cause of death, and survival status until the end of the study are recorded.

Categorical data were compared using Chi-squared or Fisher's exact test for small size data sets. Continuous data were compared between groups using unpaired t-tests. Cancer-related mortality was calculated and follow-up period was determined from the date of diagnosis to the date of cancer-related mortality of the last follow-up survivor. Survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test.⁹ A multivariate Cox-proportional hazards regression model was used to estimate mortality risk. All statistical analyses were performed using SPSS version 17.0 statistical software (SPSS Inc., Chicago, IL). A *P* value < 0.05 was considered statistically significant in all tests.

RESULTS

Table 1 shows the clinical features of PTC with DM according to the timing of DM diagnosis. After a mean follow-up period of 10.1 ± 0.9 years, the disease-specific mortality and remission rates were 70.0% (49 patients) and 10% (7 patients), respectively. Of the 70 patients with DM, DM diagnosis by biopsies were obtained before thyroidectomy in 8 patients in group A including 7 patients with bone metastases

TABLE 1. Clinical Features of Papillary Thyroid Carcinoma Patients With Distant Metastases Diagnosed at Time of Initial Thyroidectomy (Group A) or Follow-Up Period (Group B)

Clinical Characteristic	Group A (n = 40)	Group B (n = 30)	Total (n = 70)	P Value
Gender, female	24 (60.0%)	17 (56.7%)	41 (58.6%)	0.7793
Age at diagnosis (y)	52.2 ± 18.2	53.3 ± 14.3	52.7 ± 16.6	0.7855
Mean tumor size (cm)	4.0 ± 0.3	3.8 ± 0.4	3.9 ± 0.3	0.7329
Postoperative mean serum thyroglobulin level (ng/mL)	1346 ± 382	99.2 ± 55.4	772 ± 221	0.0040
Operative method				–
Total thyroidectomy	14	11	25 (35.7%)	
With lymph node dissection	15	14	29 (41.4%)	
With limited radical neck dissection	11	5	16 (22.9%)	
TNM stage				–
Stage I	0	8	8 (11.4%)	
Stage II	14	2	16 (22.9%)	
Stage III	0	6	6 (8.6%)	
Stage IV	26	14	40 (57.1%)	
¹³¹ I accumulative dose (mCi)	689 ± 115	668 ± 76	679.0 ± 70.2	0.8847
¹³¹ I avid, positive	31 (77.5%)	20 (66.7%)	51 (72.9%)	0.3131
Remission	5 (14.7%)	2 (6.7%)	7 (10.0%)	0.6873
Distant metastatic site, bone/nonbone	15/25	6/24	21/49	0.1088
Cancer mortality	27(67.5%)	22 (73.3%)	49 (70.0%)	0.5982
Follow-up period (y)	8.1 ± 1.3 [range: 0.1–31.9, medium: 4.2]	12.7 ± 0.9 [range: 3.2–26.0, medium: 12.0]	10.1 ± 0.9 [range: 0.1–31.9, medium: 11.3]	0.0100
Time interval of thyroidectomy to diagnosis of distant metastasis (y)	0.26 ± 0.10 [range: 0.1–31.9, medium: 0.2]	8.0 ± 0.8 [range: 1.3–17.5, medium: 6.8]	3.6 ± 0.6 [range: 0.1–31.9, medium: 0.6]	0.0001
Time interval from distant metastasis finding to censored point (y)	7.8 ± 1.3 [range: 0.1–31.9, medium: 4.0]	4.7 ± 0.7 [range: 0.0–14.5, medium: 3.7]	6.5 ± 0.8 [range: 0.1–31.7, medium: 3.7]	0.0675
Secondary primary cancer	2 (5.0%)	7 (23.3%)	9 (12.9%)	0.0324

TNM = tumor node metastasis.

(vertebra [n = 5]; skull base [n = 1]; and chest wall [n = 1]) and 1 patient with lung metastases. Age, gender, and initial tumor size were not significantly different between groups A and B. Postoperative serum Tg level was significantly higher in group A than in group B. Although the follow-up period was longer for group B than for group A, disease-specific mortality was not significantly different between the groups.

The mean time interval from initial thyroidectomy to DM diagnosis in group B was 8.0 ± 0.8 years (range: 1.3–17.5 years; median: 6.8 years). Of the 70 patients, 9 patients presented with a secondary primary cancer including 2 patients in group A and 7 patients in group B. The percentage of patients with secondary primary cancers was higher in group B than in group A (23.3% vs. 5.0%; *P* = 0.0324). The 2 patients in group A were diagnosed with secondary malignancies before PTC diagnosis (breast cancer [n = 1]; colon cancer [n = 1]), and the 7 patients in group B were diagnosed with secondary malignancies 10.2 to 22.1 years after PTC diagnosis (2 lung cancers [n = 2]; colon cancer [n = 1]; oral cancer [n = 1]; renal transitional cell carcinoma [n = 1]; pituitary anaplastic carcinoma [n = 1]; and malignant fibrous histiocytoma [n = 1]). In group B, the mean accumulated ¹³¹I dose was higher in the 7 PTC patients with a secondary primary cancer than in those without a secondary primary cancer (950 ± 197 mCi vs. 583 ± 73 mCi); however, this difference was not statistically significant

(*P* = 0.1105). There was less ¹³¹I avid percentage of patients in group B. Otherwise, the difference was without statistical difference, either (Table 1).

After a mean follow-up of 7.5 ± 1.0 years, 49 patients had died of thyroid cancer (Table 2). The percentage of male and older patients and patients with larger tumor size was significantly higher in the mortality group than in the survival group, whereas the percentage of patients with ¹³¹I avid metastatic lesions (first DM) was lower in the mortality group. However, postoperative Tg level and operative method were not different between the 2 groups. Patients in the survival group had significantly longer follow-up periods and had received a larger accumulated ¹³¹I dose (Table 2). Of the 70 PTC patients with DM, 48 patients (68.6%) had lung metastases, 16 patients (22.9%) had bone metastases, and 6 patients (8.6%) had multiorgan metastases including lung, bone, or brain.

Table 3 shows the number, mean age, and remission and mortality rates of PTC patients with DM in groups A and B according to metastasis site. Patients in group A with lung metastasis showed better prognosis in terms of remission rate than those with bone or multiorgan metastases (16.0% vs. 7.7% and 0%). The survival rates for the patient population and groups A and B were 85.7%, 72.5%, and 96.7% at 1 year; 65.7%, 47.5%, and 90.0% at 5 years; 52.9%, 40.0%, and 70.0% at 10 years; and 21.9%, 35.0%, and 8.0% at 20 years, respectively (Figure 2A).

TABLE 2. Clinical Features of Papillary Thyroid Carcinoma Patients With Distant Metastases in Mortality and Survival Groups

Clinical Characteristic	Mortality (n = 49)	Survival (n = 21)	Total (n = 70)	P Value
Gender, female	23 (46.9%)	18 (85.7%)	41 (58.6%)	0.0025
Age at diagnosis (y)	58.8 ± 12.0	38.5 ± 17.3	52.7 ± 16.6	0.0001
Tumor size (cm)	4.3 ± 0.3	3.1 ± 0.3	3.9 ± 0.3	0.0362
Postoperative mean serum thyroglobulin level (ng/mL)	886.0 ± 290.0	583.0 ± 324.0	772.0 ± 221.0	0.5504
Thyroidectomy (total)				0.9969
Total thyroidectomy only	17 (35.4%)	8 (36.4%)	25 (35.7%)	
With lymph node dissection	20 (41.7%)	9 (40.9%)	29 (41.4%)	
With limited radical neck dissection	11 (22.9%)	5 (22.7%)	16 (22.9%)	
TNM stage, stage I	5 (10.4%)	6 (27.3%)	11 (15.7%)	–
Distant metastatic site, nonbone/bone	30/19	19/2	49/21	0.0144
¹³¹ I accumulative dose (mCi)	565 ± 74	914 ± 140	679.0 ± 70.2	0.0185
¹³¹ I avid, positive	31 (63.3%)	20 (95.2%)	51 (72.9%)	0.0058
Follow-up period (y)	7.5 ± 1.0 [range 0.1–22.0, medium: 5.8]	16.2 ± 1.2 [range 10.6–31.9, medium: 15.3]	10.1 ± 0.9 [range 0.1–31.9, medium: 11.3]	0.0001
Secondary primary cancer	7 (14.3%)	2 (9.5%)	9 (12.9%)	0.5854

TNM = tumor node metastasis.

Survival rates were not significantly different between groups A and B. However, after DM diagnosis, patients in group B had a more rapid clinical course than those in group A. In addition, the survival analysis showed that PTC patients with bone metastases had a poorer prognosis than those with lung or multiorgan metastases (Figure 2B). Multivariate regression analysis was performed to determine the association of age, gender, timing of DM diagnosis (group A vs. group B), tumor size, ¹³¹I accumulated dose, and ¹³¹I avidity at the metastatic site with disease-specific mortality. Age and male gender were independent factors associated with disease-specific mortality (Table 4).

DISCUSSION

In our study, the 10-year disease-specific survival rate of PTC with DM was 52.9%, which is consistent with recent reports.^{10,11} Age, gender, and tumor size were significantly different between the mortality and survival groups. In a larger patient series at Kuma Hospital (Kobe, Japan), age 55 years or older was found to be the strongest predictor of disease-specific

death in PTC patients with postoperative recurrence.¹² In our study, the mean time interval from thyroidectomy to DM diagnosis was 8.0 ± 0.8 years (range: 1.3–17.5 years), indicating that long-term follow-up of PTC is necessary.

The patients in our study were categorized into 2 groups according to the timing of DM diagnosis: group A, DM diagnosed before, at or close to the time of first thyroidectomy and group B, DM diagnosed during the follow-up period. After 10 years of follow-up, the disease-specific mortality rate was not significantly different between the 2 groups (67.5% vs 73.3%). The follow-up period was longer for patients in group B than for those in group A. However, if calculated from the date of DM diagnosis, the follow-up period was actually shorter for patients in group B.

The existence of gender differences in the occurrence of thyroid nodules is well known, and the prevalence of well-differentiated thyroid cancer is much higher in female patients than in male patients.¹³ However, several studies have reported that male patients have more advanced clinical presentations

TABLE 3. Site of Metastasis, Follow-up Period, Non-relapsed and Cancer Mortality in Different Group of Papillary Thyroid Carcinoma Patients with Distant Metastases

Clinical Characteristic	Number (%)	Age (y)	Follow-Up Period (y)	Period of Distant Metastases Detected (y)	Tumor Size (cm)	Remission (%)	Mortality (%)
<i>Group A: with distant metastases at diagnosis (n = 40)</i>							
Remote metastases site							
Bone	13 (33)	59.3 ± 12.9	3.2 ± 1.3	0.3 ± 0.1	4.3 ± 0.8	1 (7.7)	12 (92.3)
Lung	25 (63)	47.7 ± 19.7	10.2 ± 1.8	0.2 ± 0.1	3.8 ± 0.3	4 (16.0)	13 (52.0)
Multiorgans	2 (5)	66.0 ± 1.4	13.9 ± 8.1	0.6 ± 0.3	3.9 ± 2.1	0	2 (100)
<i>Group B: without distant metastases at diagnosis (n = 30)</i>							
Remote metastases site							
Bone	3 (10)	61.0 ± 9.6	10.9 ± 2.6	8.3 ± 1.2	3.0 ± 0.1	1 (33.3)	2 (66.7)
Lung	23 (77)	53.1 ± 14.6	12.8 ± 1.1	7.6 ± 0.9	3.7 ± 0.5	1 (4.3)	16 (69.6)
Multiorgans	4 (13)	48.8 ± 15.9	13.5 ± 2.9	9.6 ± 3.5	4.8 ± 1.8	0 (0)	4 (100)

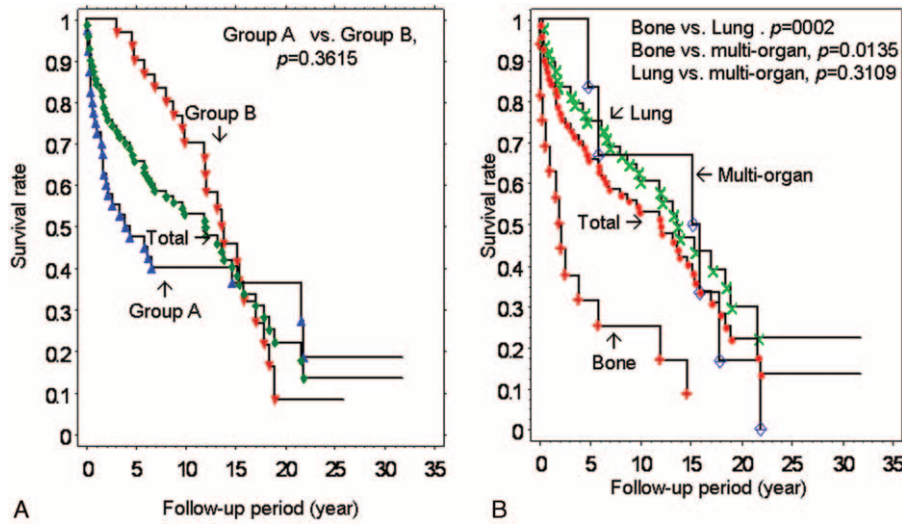


FIGURE 2. Survival rates for papillary thyroid cancer patients with distant metastasis (DM). (A) Survival rates for the patient population and patients in group A (DM diagnosed before or within 9 months after initial thyroidectomy) and in group B (DM diagnosed during the follow-up period). (B) Survival rates according to site of metastasis.

and poorer prognosis after therapy than female patients.^{14,15} Delayed diagnosis, environmental factors, and loss of estrogen receptor expression may be involved in these gender differences, although this remains controversial.¹⁶ In our study, age and male gender were important prognostic factors in both the univariate and multivariate analyses. Male gender was reported to be a risk factor for lymph node recurrence in PTC.¹⁷ However, other studies have found male gender not to be a significant prognostic factor for survival in PTC patients with DM.^{12,18,19} The clinical presentation and therapeutic outcomes of PTC vary according to geographic location, socioeconomic status, and ethnicity.^{20,21} The incidence and presentation of PTC in different ethnic groups has been well studied. In contrast, few studies have investigated the therapeutic outcomes of PTC. Differences in therapeutic methods (extent of thyroidectomy, ¹³¹I dose), ethnicity, and socioeconomic status may influence cancer mortality.²²

The site of metastases may influence treatment outcomes of PTC. The majority of thyroid cancer patients with bone metastases result in patient death.^{11,23–25} Two of our patients with bone metastasis were detected early with moderately elevated Tg levels who achieved remission status. Thyroid cancer patients with multiorgan metastases have a poor prognosis.^{10,26} In our study, 6 patients had multiorgan metastases.

Despite the longer follow-up periods, each of these patients resulted in cancer-related death. The ¹³¹I avid lesion is evidence of a well-differentiated thyroid cancer, which carries a good prognosis.¹⁰ In our study, an ¹³¹I avid lesion on the initial therapeutic scan was a significant prognostic factor for disease-specific mortality in PTC with DM in the univariate, but not multivariate, analysis.

Our study showed that secondary primary cancer can occur during the follow-up of PTC patients. Of the 9 patients with secondary primary cancer, 7 patients including 1 patient in group A and 6 patients in group B were diagnosed 10 years after the primary thyroidectomy. One of the reasons for the higher percentage of secondary primary cancer in group B was the longer follow-up period. A recent population-based study evaluating and predicting patient mortality due to thyroid cancer, other cancers, and noncancer-related conditions showed that other cancers were not associated with increased cumulative incidence of death.¹⁵ The benefit of ¹³¹I therapy in high-risk PTC patients is indisputable. However, patients receiving ¹³¹I therapy at increasing accumulated doses (eg, >1000 mCi) need to be carefully monitored for complications.²⁷ Because of the small number of patients with secondary primary cancer in our study, the association of ¹³¹I therapy with the occurrence of secondary primary cancer requires further investigation. A previous study with a

TABLE 4. Multivariate Analysis by Cox proportional Hazards Regression Model for Survival and Mortality Groups of Papillary Thyroid Carcinoma Patients with Distant Metastases

	β Coefficient	Hazard Ratio	95% Confidence Interval		P Value
			Lower Bound	Upper Bound	
Age (y)	0.037	1.037	1.011	1.064	0.0046
Sex (female vs. male)	0.682	1.977	1.022	3.826	0.0429
Tumor size (cm)	0.070	1.073	0.953	1.208	0.2472
¹³¹ I accumulative dose (mCi)	0.000	0.999	0.998	1.000	0.0391
Distant metastases site (nonbone vs bone)	0.639	1.894	0.975	3.678	0.0594
¹³¹ I avidity (negative vs positive)	0.424	1.528	0.771	3.029	0.2248

large sample size showed increased risk of both solid tumors and leukemia was found with increasing cumulative activity of ^{131}I administered.²⁸ During the follow-up period, close monitoring for the development of secondary primary cancers is mandatory. Histological type of secondary primary malignancy is influenced by ethnicity and geographical area.

Our study determined the survival and secondary cancer rates in PTC patients categorized according to the timing of their DM diagnosis. If calculate survival duration from time of DM, patients who developed DM during the follow-up period had a shorter survival than those who had DM at the time of PTC diagnosis. In addition, the percentage of patients who developed secondary primary cancers was higher in group B than in group A. Together, these findings indicate that PTC patients diagnosed with DM during follow-up have a worse prognosis. Furthermore, PTC patients require close follow-up for the occurrence of secondary primary cancers.

Our study had several limitations, including variations in the imaging techniques used during the long-term follow-up and date of DM diagnosis. Improvements in medical techniques and imaging may improve patient survival. Only a portion of the patients had pathologically verified DM. Although patients were enrolled over a 28-year period, the number of PTC patients with DM was small, which may have influenced the study results. In addition, selection bias may have affected mortality outcomes in group A patients.

In conclusion, PTC patients whose DM was diagnosed early (before or at the time of initial thyroidectomy) had higher postoperative serum Tg levels, shorter follow-up periods, and lower prevalence of secondary primary cancer compared with PTC patients whose DM was diagnosed during the follow-up period. After a mean follow-up of 10.1 years, the disease-specific mortality rate of PTC with DM was 70.0%. More aggressive treatment is warranted for older and male PTC patients with DM.

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