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Therapeutic Outcomes of Recurrent Well-Differentiated Thyroid Carcinomas

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Objective: The aim of this study was to evaluate outcomes of the recurrent and non-recurrent groups including disease-specific mortality of patients with well-differentiated thyroid carcinoma after multimodality treatment. In addition, prognostic factors for disease-specific mortality were analyzed.

Summary of Background Data: Among 2,844, there were 166 patients with recurrent disease. Recurrent disease was defined as the presence of papillary or follicular thyroid cancer 6 months after the initial thyroidectomy, including locoregional or distant metastasis, diagnosed using diagnostic or therapeutic ^{131}I scans or other imaging techniques.

Methods: The study was a retrospective analysis of prospectively collected data for a long-term follow-up result of well-differentiated thyroid carcinoma patients.

Results: The mean age of 166 patients was 45.8 ± 1.2 years, 116 (69.9%) were women, 111 (66.9%) had locoregional neck recurrence, and 55 (33.1%) had metastatic recurrence in distant organs. We found that when recurrences were observed, more than half were detected within the first 5 years following the initial therapy. The longest period of time before relapse was 29.8 years. After a mean follow-up period of 12.7 ± 0.5 years, 37 (22.3%) patients experienced disease-specific mortality. Multivariable analysis revealed that older age, male sex, and development of a second primary malignancy were associated with disease-specific mortality. Higher post-operative levels of thyroglobulin predicted a shorter time to relapse.

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Conclusions: These data indicate that among the recurrent cases over 50% of recurrent well-differentiated thyroid carcinomas were diagnosed within 5 years after initial thyroidectomy. Additionally, more than 20% of the patients died of thyroid cancer.

Key words: Total thyroidectomy – Thyroglobulin – Radioactive iodide – Disease specific mortality

The incidence of well-differentiated thyroid carcinoma has increased in developed and developing countries over the past two decades.[1–3] Most patients with well-differentiated thyroid cancer who are treated with thyroidectomy and postoperative radioactive iodine (^{131}I) remnant ablation therapy have a good prognosis.[4] However, previous studies have indicated that 10%–20% of patients are diagnosed with recurrent thyroid cancer after initial thyroidectomy.[5,6] After the initial thyroidectomy, patients with well-differentiated thyroid carcinoma may undergo ^{131}I remnant ablation, serum thyroglobulin (Tg) analysis, neck ultrasonography, or other imaging such as computed tomography (CT) scanning or 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) depending on risk stratification.[7,8] Some of these patients may be diagnosed with recurrent papillary or follicular thyroid carcinoma after the initial postoperative treatment and evaluation. However, there is a lack of information regarding long-term follow-up and therapeutic outcomes in patients with recurrent well-differentiated thyroid carcinoma. Delayed stratification of well-differentiated thyroid cancer has been suggested to identify a better correlation with recurrence. Due to the indolent clinical course of well-differentiated thyroid cancer, long-term follow-up over at least 10 years is necessary for identification of recurrences.[9,10] Management is challenging for patients with recurrent well-differentiated thyroid carcinoma. A few studies have suggested male sex, advanced stage, and the presence of initial extrathyroidal spread are predictors of recurrences.[11,12] Advances in diagnostic tools and therapeutic modalities for recurrent thyroid cancer may improve the survival rates of these patients.[13,14] However, long-term follow-up is still indicated. The purpose of this study was to identify clinical features predicting recurrence of papillary and follicular thyroid cancer after multimodality treatment. In addition, therapeutic outcomes and prognostic factors of recurrent with nonrecurrent patients were analyzed.

Patients and methods

A total of 3,656 patients with papillary or follicular thyroid carcinoma underwent thyroidectomy and received regular follow-up care at the Chang Gung Medical Center in Linkou, Taiwan, between 1977 and 2013 (Fig. 1). Among 3,656 patients, 2,844 cases were enrolled in the study. Cases of lost follow-up and initial operation in other hospitals were excluded. Tumors were staged following the initial thyroidectomy based on the Union for International Cancer Control tumor-node-metastasis (TNM) criteria (6th edition).[15] In this study, patients between 2010 and 2013, the 6th edition of TNM stage were used too. The pathologic classification of all thyroid carcinoma tissues was performed according to the World Health Organization criteria.[16]

We recommended that thyroid cancer patients with an intermediate or high risk of recurrence undergo thyroid ^{131}I remnant ablation 4–6 weeks after the initial thyroidectomy.[5] The dose of ^{131}I ablation for most patients was 1.1–3.7 GBq (30–100 mCi). One week after ^{131}I administration, a whole-body scan (WBS) was performed using a dual-head gamma camera (Siemens Medical Solutions USA, Inc., Malvern, PA, USA). Whole-body images were acquired using continuous mode scanning at a speed of 5 cm/min. In addition, thyroid scintigraphy was performed using a pinhole collimator with a 4-mm aperture placed 7 cm above the neck for 50,000 counts for 30 minutes. Levothyroxine treatment was initiated to decrease thyroid-stimulating hormone levels without inducing clinical thyrotoxicosis. Cases where ^{131}I uptake extended beyond the thyroid bed were classified as residual disease or metastasis unless the results were proven to be false positives. Higher therapeutic doses of 3.7–7.4 GBq (100–200 mCi) were administered to patients with persistent disease. Patients who received doses exceeding 1.1 GBq were isolated upon hospital admission. A WBS was performed 2 weeks after the administration of higher therapeutic doses of ^{131}I. In cases of distant metastasis detected by ^{131}I

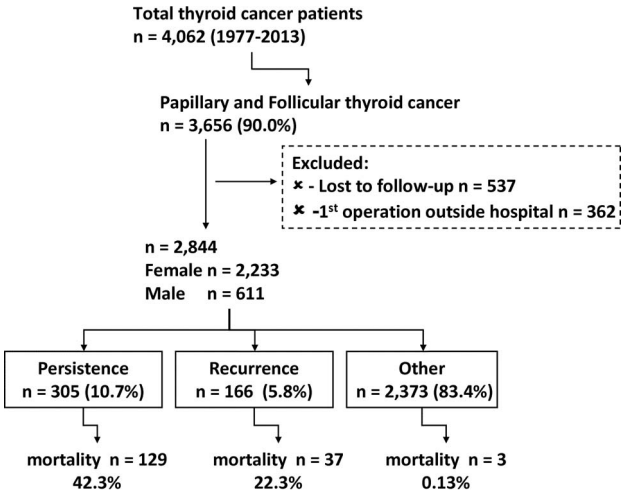

Fig. 1 Flow chart showing the classification of thyroid cancer patients. The numbers of patients with recurrent papillary or follicular thyroid carcinoma who were treated between 1977 and 2013 are shown.

or nonremission, a repeat high therapeutic dose of ^{131}I was recommended every 6–12 months.

Neck ultrasonography was performed 6–12 months after the initial thyroidectomy to exclude the possibility of local recurrence. We defined recurrent disease as the presence of papillary or follicular thyroid cancer 6 months or longer after the initial thyroidectomy. All of the patients with recurrent disease were without evidence of well-differentiated thyroid cancer in the locoregional neck or distant metastasis on the first postoperative ^{131}I ablation scan and other noninvasive imaging studies.

Recurrent disease included locoregional or distant metastasis and was diagnosed using diagnostic or therapeutic ^{131}I scans or other imaging techniques (they may or may not have been cytologically proven). Recurrent tumors were not included if they were diagnosed post-operatively on diagnostic or therapeutic ^{131}I scans, or if they were non-resectable. In contrast, persistent disease was diagnosed postoperatively on diagnostic or therapeutic ^{131}I scans or other imaging studies, including cases that were nonresectable. For analysis of the therapeutic outcomes, all data on therapeutic outcomes was closed at the end of 2014. Patients were classified into disease-specific mortality (DSM), nonremission, and remission groups. DSM was the patients died of thyroid cancer. The remission group consisted of patients with negative ^{131}I WBS results and no evidence of local or distant metastasis upon noninvasive examination.

Serum thyroglobulin (Tg) levels were measured using an immunoradiometric assay (CIS Bio International, Gif-sur-Yvette, France). The detection limit of the Tg kit was 0.5 ng/mL. The functional sensitivity of this assay was assessed in our laboratory and was found to be 1.2 ng/mL. Tg antibody levels were measured using a competitive radioimmunoassay (Biocode, Liège, Belgium). The analytical sensitivity of this assay was 6 IU/mL.

Unpaired *t* tests were used to compare continuous data between groups. Categoric data were compared using chi-square or Fisher's exact tests for small data sets. We calculated the DSM rate for patients that died of thyroid cancer. The follow-up period was defined as the time from the date following surgery and the first ^{131}I ablation to the date of DSM. Survival rates were calculated using the Kaplan-Meier method and compared using log-rank tests.[17] A multivariable Cox proportional hazard regression model was used to estimate the mortality risk. All statistical analyses were performed using SPSS version 17.0 statistical software (SPSS Inc., Chicago, IL, USA). A P value < 0.05 was defined as statistically significant in all tests. The Chang Gung Medical Foundation Institutional Review Board (104-3901B) approved this study. The requirement for informed consent was waived because of the retrospective nature of the study.

Results

Of the 2,844 patients with papillary or follicular thyroid carcinoma, 305 (10.7%) had persistent cancer after initial thyroidectomy and ^{131}I remnant ablation therapy, which included local residual disease and distant metastasis (Fig. 1). Six months after the initial thyroidectomy, 166 patients presented with recurrent disease. These 166 patients included 146 patients with papillary thyroid carcinoma and 20 with follicular thyroid carcinoma. The mean age of these patients was 45.8 $\pm$ 1.2 years and 116 of the patients were women (69.9%). There was no evidence of local recurrence or distant metastasis in these patients upon imaging within 6 months of the initial thyroidectomy. Among the patients with recurrence, 95 (57.2%) underwent a second locoregional resection, which included 28 patients who underwent locoregional resection two or more times. Of the 95 cases that underwent a second locoregional resection, lymph node dissection was performed in 65 cases (68.4%) only; and, soft tissue

Table 1 Clinical features of papillary or follicular thyroid cancer in recurrence or non-recurrence groups

Clinical characteristics	Recurrence number (%)	Nonrecurrence number (%)	*P* value
Patient number	166 (5.8)	2,373 (83.4)	
Gender, female	116 (69.9)	1,920 (80.9)	0.001
Age at diagnosis (y)[a]	45.8 ± 1.2	42.9 ± 0.3	0.007
Mean tumor size (cm)[a]	3.2 ± 0.1	2.2 ± 0.0	< 0.001[b]
Postoperative serum Tg level after 1 month (ng/mL)[a]	180.9 ± 56.0	21.6 ± 1.9	< 0.001[b]
Multifocality	50 (30.1)	519 (21.9)	0.014
Operative method			
Total thyroidectomy	154 (92.8)	2,007 (84.6)	0.004
Less than total thyroidectomy	12 (7.2)	366 (15.4)	
Histology			
Papillary	146 (88.0)	2,189 (92.2)	0.049
Follicular	20 (12.0)	184 (7.8)	
TNM stage			
Stage I	78 (47.0)	1,780 (75.0)	< 0.001
Stage II	16 (9.6)	221 (9.3)	0.889
Stage III	22 (13.3)	181 (7.6)	0.010
Stage IV	50 (30.1)	191 (8.0)	< 0.001
Follow-up period (y)[a]	12.7 ± 0.5	9.8 ± 0.1	< 0.001
Postoperative ^{131}I cumulative dose (mCi)[a]	403.1 ± 24.0	103.8 ± 2.3	< 0.001
External beam radiation therapy	**33 (19.9)**[b]	**21 (0.9)**	< **0.001**
Remission	29 (17.5)	1,049 (44.3)	< 0.001
2nd primary cancer	10 (6.0)	83 (3.5)	0.144
Overall mortality	41 (24.7)	117 (4.9)	< 0.001
Disease specific mortality	37 (22.3)	3 (0.1)	< 0.001

[a]Mean ± standard error (SE).

[b]Twenty-one cases underwent external beam radiation therapy after recurrence.

and thyroid bed was involved in other cases. Seven patients underwent resection for distant metastases, which included metastasis to the lungs, bones, and brain. There were 164 patients who underwent ^{131}I remnant ablation and received additional therapy.

A comparison of the clinical features of the patients in the recurrent and nonrecurrent groups (2,373 patients) revealed that patients in the recurrent group were more likely to be male, be older, and have high postoperative serum Tg levels, multifocal tumors, follicular thyroid cancer, and advanced TNM stage. There was a lower percentage of patients in remission in this group, which had higher DSM compared to patients in the nonrecurrent group (Table 1). Multiple regression analysis indicated that only tumor size and postoperative serum Tg level significantly differed between the groups ($P < 0.05$).

The clinical features of the 166 patients with well-differentiated thyroid carcinoma are shown in Table 2. The patients with follicular thyroid carcinoma were generally older, had larger tumors, had higher mean postoperative serum Tg levels, and a more advanced TNM stage compared to patients with papillary thyroid carcinoma. Of the 166 patients with recurrence, 111 (66.9%) had locoregional tumor growth and 55 (33.1%) had distant metastasis. However, 32 of 111 patients (28.8%) with locoregional tumors developed distant metastasis during the follow-up period. After the mean follow-up period of 12.7 ± 0.5 years, 37 (22.3%) patients died of thyroid cancer. The mean survival time was 12.3 years. Patients with follicular thyroid carcinoma had a higher rate of cancer mortality compared to patients with papillary thyroid carcinoma. However, the difference was not statistically significant (35.0% versus 20.5%; $P = 0.145$).

Recurrence could be diagnosed at any time during the follow-up period (from 6 months to 29.8 years after the initial thyroidectomy). The mean time to tumor recurrence was 5.6 ± 0.4 years. The patient numbers and time until relapse are shown in Fig. 2. When recurrences were observed, more than half (59%) were detected within the first 5 years following the initial therapy. The longest remission period before recurrence was 29.8 years in a 31-year-old woman, who was diagnosed with papillary thyroid carcinoma with a 2.5 cm tumor. This patient did not present with grossly enlarged lymph nodes. Therefore, she underwent a partial thyroidectomy in 1980 and was treated with thyroid hormone replacement therapy. This patient had an unstimu-

Table 2 Clinical features of relapsed thyroid cancer in papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC)

Clinical characteristics	All patients	PTC versus FTC		
		PTC number (%)	FTC number (%)	*P* value
Patient number	166 (100.0)	146 (88.0)	20 (12.0)	
Gender, female	116 (69.9)	103 (70.5)	13 (65.0)	0.612
Age at diagnosis (y)[a]	45.8 ± 1.2	44.9 ± 1.2	52.3 ± 3.2	0.044
Mean tumor size (cm) [a]	3.2 ± 0.1	3.0 ± 0.2	4.7 ± 0.4	<0.001
1-month postoperative serum Tg level (ng/mL) [a]	180.9 ± 56.0	111.1 ± 19.0	706.2 ± 437.1	0.001
Multifocality	50 (30.1)	47 (32.2)	3 (15.0)	0.116
Operative method				
Total thyroidectomy	154 (92.8)	136 (93.2)	18 (90.0)	0.610
Less than total thyroidectomy	12 (7.2)	10 (6.8)	2 (10.0)	
TNM stage				
Stage I	78 (47.0)	74 (50.7)	4 (20.0)	0.001
Stage II	16 (9.6)	10 (6.8)	6 (30.0)	
Stage III	22 (13.3)	17 (11.6)	5 (25.0)	
Stage IV	50 (30.1)	45 (30.8)	5 (25.0)	
Recurrent site				
Local region	111 (66.9)	104 (71.2)	7 (35.0)	0.001
Distant metastasis	55 (33.1)	42 (28.8)	13 (65.0)	
Follow-up period (year)[a]	12.7 ± 0.5	12.7 ± 0.6	12.4 ± 1.4	0.828
Relapsed period (year)[a]	5.6 ± 0.4	5.4 ± 0.4	7.2 ± 1.2	0.128
Post-operative ^{131}I cumulative dose (mCi)[a]	403.1 ± 24.0	411.5 ± 26.3	342.3 ± 52.5	0.352
Radiation therapy	33 (19.9)	26 (17.8)	7 (35.0)	0.071
Remission	29 (17.5)	25 (17.1)	4 (20.0)	0.751
2nd primary cancer	10 (6.0)	10 (6.8)	0 (0.0)	0.611
Overall mortality	41 (24.7)	33 (22.6)	8 (40.0)	0.091
Disease specific mortality	37 (22.3)	30 (20.5)	7 (35.0)	0.145

[a]Mean ± SE.

lated Tg level of 7.4–10.5 ng/mL. A locoregional neck nodule was detected in the left lower paratracheal lateral neck in 2009. A histologic examination revealed that the nodule was a papillary thyroid carcinoma with fibroadipose tissue and skeletal muscle infiltration. Therefore, the patient underwent a second neck surgery. In 2011, lung metastasis was detected in on a ^{131}I therapeutic scan. The patient is currently undergoing regular follow-up care.

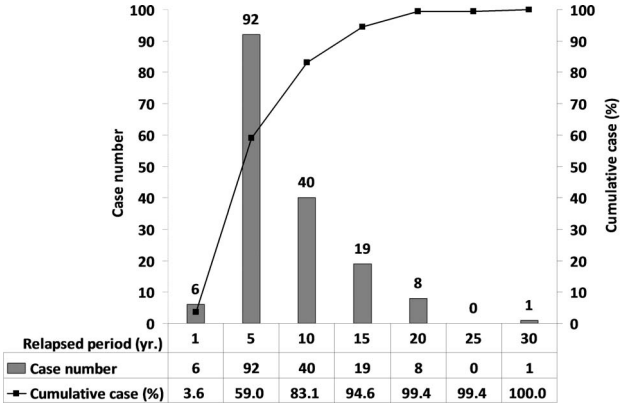

Fig. 2 Cumulative number and percentage of patients with recurrent papillary or thyroid carcinoma 6 months after initial thyroidectomy.

The clinical features of patients with recurrent well-differentiated thyroid cancer categorized into survival and DSM groups are shown in Table 3. Patients in the DSM group were more likely to be male, had larger tumors and advanced TNM stage, were older, and were more likely to have a second primary tumor. There were no significant differences in histologic type, therapeutic strategy, surgical method, or initial and accumulated ^{131}I dose between the DSM and survival groups. Multivariable analysis revealed statistically significant differences in age, sex, tumor size, multifocality, and second primary malignancy between the groups (Table 4). A total of 10 patients (6.0%) were diagnosed with secondary primary malignancies. At the end of the follow-up period, 5 out of 10 patients with second primary malignancies had died of thyroid cancer and one patient had died of gastric cancer. The disease-specific survival rates for patients with recurrent thyroid carcinoma were 96.9%, 87.9%, and 62.0% at 5, 10, and 20 years, respectively. The difference in the DSM rate between patients with papillary and follicular thyroid carci-

Table 3 Clinical features of recurrent thyroid cancer in disease-specific mortality (DSM) or survival groups

Clinical characteristics	DSM number (%)	Survival[a] number (%)	*P* value
Patient number	37 (22.3)	129 (77.7)	
Gender, female	18 (48.6)	98 (76.0)	0.001
Age at diagnosis (y)[b]	55.2 ± 1.9	43.1 ± 1.3	<0.001
Mean tumor size (cm)[b]	4.1 ± 0.4	2.9 ± 0.1	0.001
Post-operative serum Tg level after 1 m (ng/mL)[b] [range]	367.8 ± 244.2 [0.0-8470.0]	129.4 ± 21.8 [0.0-1657.0]	0.0807
Multifocality	5 (13.5)	45 (34.4)	0.012
Operative method			
Total thyroidectomy	34 (91.9)	120 (93.0)	0.815
Less than total thyroidectomy	3 (8.1)	9 (7.0)	
Histology			
Papillary	30 (81.1)	116 (89.9)	0.145
Follicular	7 (18.9)	13 (10.1)	
TNM stage			
Stage I	8 (21.6)	70 (54.3)	0.004
Stage II	5 (13.5)	11 (8.5)	
Stage III	9 (24.3)	13 (10.1)	
Stage IV	15 (40.5)	35 (27.1)	
Recurrent site			
Local region	25 (67.6)	86 (66.7)	0.918
Distant metastasis	12 (32.4)	43 (33.3)	
Follow-up period (year)[b]	10.7 ± 0.9	13.3 ± 0.6	0.045
Post-operative ^{131}I accumulative dose (mCi)[b]	453.7 ± 60.0	388.6 ± 25.6	0.263
Remission	-	29 (22.5)	0.002
Radiation therapy	20 (54.1)	13 (10.1)	<0.001
2nd primary cancer	5 (13.5)	5 (3.9)	0.045

[a]Includes non-disease-specific mortality (4 patients).

[b]Mean ± SE.

noma was not statistically significant ($P = 0.2051$) (Fig. 3).

To understand the effect of the postoperative stimulated serum Tg level on therapeutic outcomes, patients with thyroid cancer recurrence were classified into 3 groups according to Tg level (Table 5). We excluded 12 patients who tested positive for anti-Tg antibodies, 12 patients who had undergone partial thyroidectomy or lobectomy, and 4 patients without data regarding postoperative Tg levels. Post-operative Tg levels were significantly higher in patients with papillary thyroid carcinoma, advanced TNM stage, shorter times to recurrence, and a lower rate of remission. However, the differences in postoperative serum Tg levels were not statistically significant when DSM and total mortality were considered in patients with recurrent disease (Table 5).

Discussion

Most well-differentiated thyroid carcinomas are indolent malignancies. There are a few studies of well-differentiated thyroid cancer patients with a mean follow-up period over 10 years similar to our investigation. In our study, 16.5% of patients with papillary and follicular thyroid carcinoma devel-

Table 4 Multivariate analysis by Cox proportional hazards regression model for survival and disease-specific mortality

				95% CI for Exp (B)	
Factors	β coefficient	Hazard ratio	*P* value	Lower	Upper
Age at diagnosis (y)	0.0171	1.0173	<0.0001	1.0137	1.0209
Gender, male versus female	0.1467	1.1581	0.0048	1.0458	1.2823
Tumor size (cm)	−0.0804	0.9227	<0.0001	0.8963	0.9499
Multifocality (non versus multifocality)	0.5190	1.6804	<0.0001	1.5232	1.8538
TNM stage	−0.0116	0.9885	0.6394	0.9417	1.0376
2nd primary cancer	−0.5791	0.5604	<0.0001	0.4508	0.6966

95% CI: confidence interval.

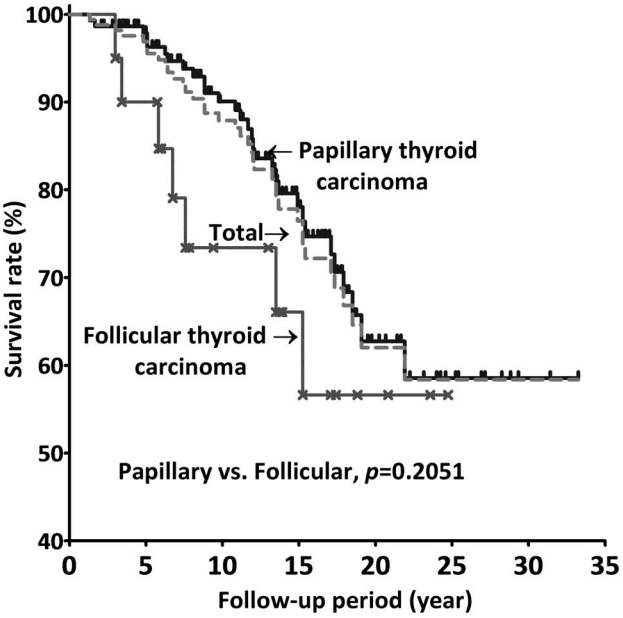

Fig. 3 Thyroid cancer-specific survival rates for patients with total recurrent well-differentiated papillary and follicular thyroid carcinoma.

oped postoperative persistent or recurrent disease. We have previously shown that a shorter time to recurrence predicts a worse outcome (i.e., shorter disease-specific survival).[5] In this study, we focused on patients diagnosed with recurrent disease within 6 months after the initial thyroidectomy. Patients with recurrent thyroid cancer were considered to be in remission after the initial thyroidectomy and thyroid remnant ablation.

Thyroidectomy is the most important step in the treatment of papillary and follicular thyroid carcinomas. It is important to note that surgical methods are dependent upon the stratification of patients with thyroid cancer.[6,18] In our study, 10.7% of patients presented with persistent cancer after surgery. These patients included those with locoregional and nonresectable or distant metastases that were detected via postoperative ^{131}I scans or other imaging techniques.[5,19] This group of patients was classified as structure incomplete or high risk according to the American Thyroid Association (ATA) guidelines,[6] and showed a high rate of DSM (42.3%) on long-term follow-up.

Most patients with recurrent thyroid cancer in this study were in the intermediate risk and biochemical incomplete groups based on the ATA

Table 5 Clinical features of relapsed thyroid cancer in different 1-month postoperative serum Tg level groups (ng/mL)

Clinical characteristic	All patients[a]	Tg < 1.2 number (%)	1.2 ≤ Tg < 10 number (%)	Tg ≥ 10 number (%)	*P* value
Patient number	139	12 (8.6)	33 (23.7)	94 (67.6)	
Gender					
female	95	11 (11.6)	25 (26.3)	59 (62.1)	0.074
male	44	1 (2.3)	8 (18.2)	35 (79.5)	
Age at diagnosis (y)[b]	45.8 ± 1.3	46.8 ± 4.2	48.4 ± 2.7	44.7 ± 1.6	0.486
Mean tumor size (cm)[b]	3.1 ± 0.1	3.2 ± 0.4	2.8 ± 0.2	3.2 ± 0.2	0.549
Multifocality	44	1 (2.3)	11 (25.0)	32 (72.7)	0.191
Histology					
Papillary	122	7 (5.7)	31 (25.4)	84 (68.9)	0.004
Follicular	17	5 (29.4)	2 (11.8)	10 (58.8)	
TNM stage					
Stage I	63	2 (3.2)	13 (20.6)	48 (76.2)	0.020
Stage II	13	4 (30.8)	5 (38.5)	4 (30.8)	
Stage III	17	2 (11.8)	5 (29.4)	10 (58.8)	
Stage IV	46	4 (8.7)	10 (21.7)	32 (69.6)	
Follow-up period (y)[b]	12.4 ± 0.6	14.4 ± 1.9	14.5 ± 1.3	11.5 ± 0.6	0.046
Relapsed period (y)[b]	4.9 ± 0.3	7.6 ± 1.6	5.3 ± 0.7	4.5 ± 0.4	0.039
Post-operative ^{131}I cumulative dose (mCi)[b]	423.0 ± 26.9	299.6 ± 56.6	433.3 ± 72.7	435.2 ± 29.3	0.376
2nd primary cancer	8	0 (0.0)	3 (37.5)	5 (62.5)	0.469
Remission	26 (18.7%)	6 (50%)	11 (33.3%)	9 (9.6%)	<0.001
Disease-specific mortality	31	3 (9.7)	9 (29.0)	19 (61.3)	0.685
Overall mortality	34	3 (8.8)	10 (29.4)	21 (61.8)	0.657

[a]Excludes patients with no Tg data available who were anti-Tg antibody-positive, or who underwent less than total thyroidectomy: (n = 27 patients).

[b]Mean ± SE.

guidelines.[6] We found that 5.8% of patients with well-differentiated thyroid carcinoma presented with recurrent cancer 6 months after the initial thyroidectomy, with or without ^{131}I remnant ablation. The time to recurrence and other prognostic factors are important during long-term follow-up of patients with well-differentiated thyroid carcinoma.[20–22] We determined that patients with well-differentiated thyroid carcinoma who are not postoperatively diagnosed with persistent disease within the first 6 months should be closely monitored for 5 years since among the cases of recurrence nearly 60% of patients are diagnosed with recurrence within this time period. After the mean follow-up of 12.7 $\pm$ 0.5 years, recurrence resulted in DSM in 37 out of 166 patients (22.3%). We estimated that DSM occurred in 1.30% of recurrent cases (2,844 cases). This result is similar to that reported by the Memorial Sloan Kettering Cancer Center for disease-related deaths in patients with well-differentiated thyroid carcinoma (1.3%) who were considered free of macroscopic disease after initial treatment.[23]

In our study, follicular thyroid carcinoma was higher DSM and overall mortality than papillary thyroid carcinoma. However, the difference did not reach statistical difference. The main cause was delayed diagnosis of follicular thyroid carcinoma, which presented with larger tumor size and advanced TNM stage. The postoperative serum Tg level is a prognostic and stratification factor for patients with well-differentiated thyroid cancer.[24–27] In our study, the serum Tg level was not found to be a prognostic factor for DSM in patients with recurrent, well-differentiated thyroid cancer. However, higher serum Tg levels were associated with a shorter time to recurrence. Lower postoperative serum Tg levels have been associated with higher disease-free survival after appropriate treatment. Patients who have abnormally high Tg levels should be monitored closely during the follow-up period. Patients with well-differentiated thyroid carcinoma who were treated with complete thyroidectomy and remnant ablation and who had no metastatic lesions (not detectable via ^{131}I WBS) and undetectable serum Tg levels were considered disease free after treatment. Among the patients with recurrent disease, 12 had undetectable Tg levels within a mean period of 7.6 years. This may be explained by limitations in the sensitivity of the Tg assay kit.

We found that age, male sex, tumor size, and TNM stage were risk factors for thyroid cancer recurrence and DSM. In contrast, postoperative serum Tg levels and histologic patterns were found to be risk factors for recurrence but not for mortality.[28,29] There is some controversy regarding the role of sex in the disease-specific survival rate of patients with well-differentiated thyroid cancer.[30,31] In this study, male patients had a worse prognosis than female patients, who may have a higher prevalence of thyroid nodules or thyroid cancer. However, male patients with well-differentiated thyroid cancer who had a high risk of recurrence usually had poor therapeutic outcomes.

Most patients with well-differentiated thyroid cancer undergo long-term follow-up treatment. During this period, the development of a second primary tumor should be considered in the differential diagnosis and treatment of these patients.[32,33] The presence of a second primary malignancy is an important prognostic factor that is associated with poor outcomes in patients with recurrent thyroid cancer. In this study, 7.8% of the patients who had a relapse were diagnosed with a second primary tumor. Most of these patients were diagnosed after presenting with thyroid and metachronous cancer. There were no organ-specific histopathologic patterns. During long-term follow-up, a differential diagnosis of thyroid cancer recurrence was mandatory. In this study, 29 patients (17.5%) with recurrent disease (after initial thyroidectomy and ^{131}I remnant ablation therapy) were treated until they were disease free with undetectable stimulated Tg levels in serum. In our study, we had enrolled enough cases for analysis and the follow-up period was long enough. However, there were limitations in our long-term follow-up study, including the 6th edition of UICC used. During this long term follow-up study, therapeutic interventions and surgical technique may change over time. In the early period, most papillary microcarcinomas underwent total thyroidectomy. However, in the last 10 years a less aggressive surgical procedure was performed for this low-risk group. Serum Tg assay was performed since 1986 in our medical center. Although thyroid ultrasonography was performed since 1985, B-mode was used with low sensitivity in the first 5 years.

Conclusions

Recurrent well-differentiated thyroid cancer was not unusual during long-term follow-up of these patients. More than 25% of patients experienced DSM after appropriate diagnosis and treatment. Older male patients with a second primary malignancy need to be monitored closely during follow-up and should be treated aggressively.

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