Determinants of Worsening Response to Therapy in Patients Diagnosed With Papillary Thyroid Carcinoma in a Tertiary Hospital

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ABSTRACT

Introduction: Papillary thyroid cancer (PTC) is generally considered to be an indolent disease with relatively good prognosis. However, some studies have shown that the Filipino population has a higher risk for disease recurrence compared to non-Filipino patients and hence early identification and management during the follow-up period would be beneficial, especially those in whom risk factors for recurrence were identified.

Objective: This study aims to identify determinants for disease recurrence of patients with papillary thyroid carcinoma (as defined by the American Thyroid Association (ATA) guidelines 2015) diagnosed from January 1, 2013-December 31, 2017, seen at the University of Santo Tomas Hospital (USTH) outpatient endocrine clinic and underwent total thyroidectomy with or without radioactive iodine ablation therapy.

Methodology: Retrospective review of outpatient medical records of 82 patients with PTC who underwent total thyroidectomy with or without radioactive iodine (RAI) therapy and achieved excellent response (ER) to therapy was performed. Baseline clinical profile such as age at diagnosis, sex, family history of thyroid cancer, family history of goiter, histopathology result, serial thyroglobulin (Tg), anti-thyroglobulin (anti-Tg) levels, whole body scan reports, neck ultrasound reports and RAI doses were collected. Logistic regression analysis was used to identify determinants to the development of worsening response.

Results: Of the 82 patients, 18 (21.9%) developed worsening response to therapy. Predictors of poor outcomes identified from previous studies such as age, sex, extent of disease, size and multifocality of tumors, ATA risk classification and initial dynamic risk assessment, RAI therapy, level of thyroid-stimulating hormone (TSH) suppression were analyzed. After logistic regression analysis, there was no significant association between variables and progression to worsening response that were previously identified in other studies.

Conclusion: Even though no significant association between investigated variables and worsening response were identified in this study, previous studies with larger populations that had exhibited positive association should be considered and hence current Philippine guidelines for the management of PTC must still be applied.

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INTRODUCTION

Well-differentiated thyroid carcinoma (WDTC) is the most common type of thyroid malignancy composed of papillary and follicular thyroid cancers and is generally considered to have good prognoses. In a study done at the Philippine General Hospital (PGH) published in 2016, a total of 649 (89%) out of 728 patients diagnosed with WDTC showed papillary thyroid cancer (PTC) in the final histopathology, whereas 79 (11%) are follicular thyroid carcinoma. [1] This was consistent with earlier studies in which PTC was found to be the most common type of WDTC comprising of approximately 88% of all thyroid malignancies in the United States with 10-year survival rates of >90%.[2,3] However, despite demonstrating satisfactory long-term outcomes, one study from Taiwan reported that PTC has a recurrence rate of 7.2% in early stage disease (stage I and II) and 28.2% in advanced stage disease (stage III and IV).[10]

Another study from the PGH had shown that 35.17% of Filipinos with low-risk PTC (defined by the American Thyroid Association guidelines 2009) had disease recurrence owing to a larger tumor diameter and family history of PTC, while radioactive iodine (RAI) therapy and initial thyroglobulin (Tg) levels ≤2 ng/mL, and an initial anti-thyroglobulin (anti-Tg) level ≤50 U/mL significantly protected patients from disease recurrence.[4] Kus, et al., concluded that Filipinos have higher risk for disease recurrence with an incidence of 25% compared with 9.5% incidence in non-Filipino patients.[5] In 2012, the PGH released revised clinical practice guidelines (CPG) for the management of WDTC and reported that patients who underwent less than total or near-total thyroidectomy had higher incidence of recurrence. It was emphasized that since many patients were lost to follow-up after initial surgical management, a more aggressive initial surgical approach improved survival for high-risk patients and decreased recurrence rates even for low-risk patients.[6] Furthermore, previous studies have described patients who were initially stratified as low risk to have higher relative risk of disease persistence biochemically as manifested by isolated hyperthyroglobulinemia without identifiable structural disease while intermediate- to high-risk patients were more likely to manifest structural persistence/recurrence.[7]

The 2015 ATA guidelines for diagnosis and management of differentiated thyroid carcinoma adapted four treatment responses during dynamic risk stratification (DRS) for every clinic visit and it was adapted by the 2021 Philippine Interim Guidelines for the Diagnosis and Management of Well-Differentiated Thyroid Cancer which include: excellent response, biochemical incomplete response, structural incomplete response and indeterminate response (IR). Parameters include levels of serial stimulated/unstimulated Tg, anti-Tg and neck ultrasound with additional whole body scan if clinically warranted.[7] Subsequent patient follow-up and management approaches were determined using these treatment response assessments with the aim of ensuring disease-free states or early detection of disease recurrence and prompt management.

Objective of the study

The objective of this study is to identify determinants for disease recurrence of patients with papillary thyroid carcinoma (as defined by the American Thyroid Association guidelines 2015) diagnosed from January 1, 2013-December 31, 2017, seen at the University of Santo Tomas Hospital (USTH) outpatient endocrine clinic and underwent total thyroidectomy with or without radioactive iodine ablation therapy.

Significance of the study

PTC being a particularly common thyroid disease in the Filipino population has a generally good prognosis, especially when diagnosed at an early stage. Compliance to follow-up is equally important as early diagnosis to evaluate and manage for disease recurrence or monitor and prolong disease-free states.

METHODOLOGY

This is a retrospective, single-center, analytical cohort study conducted at the University of Santo Tomas Hospital (USTH). The Institutional Review Board (IRB) of the hospital approved the study design. Adult

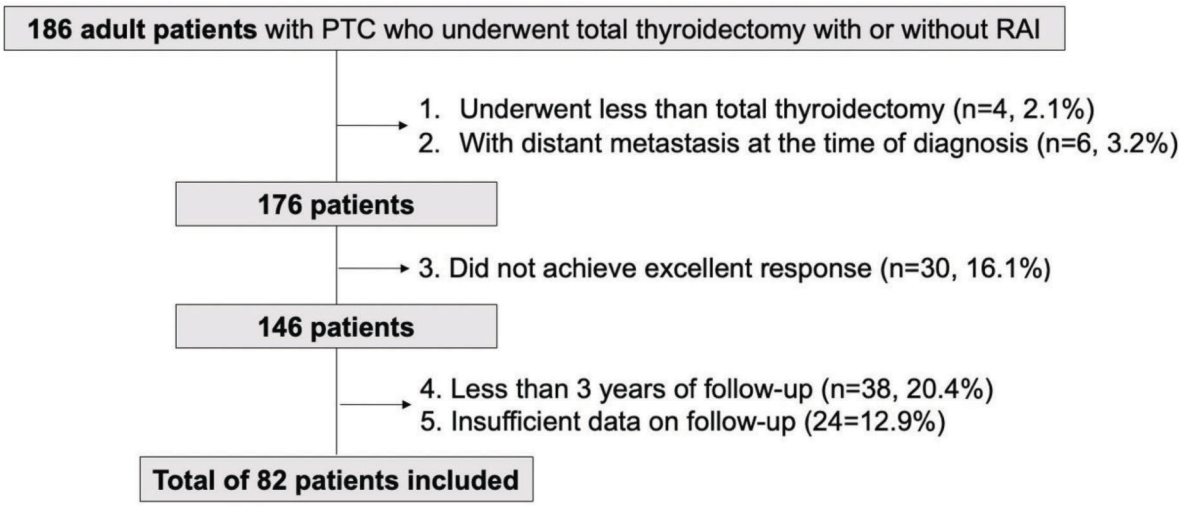

Figure 1: Study flowchart for the selection study population

patients diagnosed with PTC who underwent total thyroidectomy with or without RAI ablation therapy prior to December 31, 2019 and achieved excellent response (ER) to therapy were included. Outpatient medical records of eligible patients were reviewed from the time of diagnosis up to the latest documented follow-up of at least three years after surgery.

The DRS was utilized in this study to monitor response to therapy after achieving ER: (1) Excellent response (ER), defined as no clinical, biochemical or structural evidence of disease. (2) Biochemical recurrence (BR), defined as elevated stimulated (sTg) ≥10 ng/mL or unstimulated (uTg) ≥1 ng/mL thyroglobulin (Tg) levels or rising anti-thyroglobulin (anti-Tg) levels in the absence of localizable disease. (3) Structural recurrence (SR), defined as structural evidence of disease with any Tg level, with or without anti-Tg. (4) Indeterminate response (IR), defined as non-specific findings on imaging studies, faint uptake in thyroid bed on RAI scanning, non-stimulated Tg detectable but <1 ng/mL, or stimulated Tg detectable but <10 ng/mL, or anti-Tg antibodies stable or declining in the absence of structural or functional disease. [7,9] Development of worsening response to therapy was operationally defined as IR or BR or structural incomplete response after achieving ER to therapy at any time during follow-up. Low-risk PTC is defined as those without local or distant metastases, non-aggressive histology, intrathyroidal, encapsulated follicular variant papillary thyroid cancer, and intrathyroidal papillary microcarcinoma while intermediate-risk PTC is defined as those with microscopic invasion of tumor into the perithyroidal soft tissues, RAI-avid metastatic foci in the neck, aggressive histology, identified vascular invasion, clinical N1 or >5 pathologic N1 with all involved lymph nodes. [7,9] Those who underwent less than total thyroidectomy did not achieve ER, had distant metastases /high-risk upon diagnosis, had less than three years of follow-up or inadequate DRS on follow-up were excluded in this study.

Of the 186 records reviewed, 82 satisfied the inclusion criteria. The reasons for exclusion of 104 subjects were as follows: underwent less than total thyroidectomy (n=4, 2.1%), with distant metastases upon diagnosis (n=6, 3.2%), did not achieve ER (n=30, 16.1%), insufficient DRS (n=24, 12.9%) and less than three years of follow-up (n=38, 20.4%). Those who did not undergo RAI ablation, who were only followed with neck ultrasound that did not show suspicious findings and wherein no further follow-up biochemical testing was done, were considered to have ER.

The data gathered from outpatient medical records were age, sex, history of goiter, family history of PTC, histologic subtype, tumor size, bilaterality, multifocality, Tg levels, anti-Tg levels, post-therapy whole body scan results, neck ultrasound results, history of RAI ablation therapy, dose of RAI given, date of surgery and date of latest follow-up. The serial results of Tg, anti-Tg and imaging studies were used to interpret the DRS (ER, IR, BR, SR) as previously described. Specific dates of achievement of ER and subsequent development of worsening response (IR, BR, SR) to therapy were also documented. Based on the official histopathology report and imaging studies, patients were further subclassified into low, intermediate and high risk in developing

disease recurrence as described in the 2015 ATA risk classification. The American Joint Committee on Cancer (AJCC) 8th edition was used to characterize patient's disease stage (stage I, II, III, IVA) after initial therapy. [15] With these data, the main outcome of interest was to identify determinants of worsening response of PTC patients after achieving ER to therapy. Further association of ATA risk classification, RAI ablation therapy, median thyroid stimulating hormone (TSH) levels and development as well as time duration to development of worsening response was also investigated.

Statistical analyses will be conducted using STATA Statistical Software, Version 13, College Station, TX: College Station, TX: StataCorp LP. A *p*-value of 0.05 will be considered statistically significant. Descriptive statistics include mean and standard deviation as well as frequency and percentage depending on the level of data measurement. Comparative analyses of demographic and clinical characteristics according to worsening response therapy status, type of worsening response to therapy and time duration to worsening response to therapy will be performed using independent t-test, for continuous variables and Chi-Square test of Homogeneity or Fisher's Exact Test, if the assumption of at least five expected frequencies per cell was not met (Daniel & Cross, 2013).

RESULTS

The baseline clinical profile of all patients is reported in Table 1. Out of 82 patients included, 78 (95.12%) were female and 54 (65.85%) less than 55 years of age. Twenty-six percent had a family history of goiter. Out of 77 patients with available histopathology reports, 57 (74%) showed unilateral disease whereas 9 of these patients exhibited multifocality. Fifty (64.9%) patients had tumor size less than 2 cm while only 5 (6.4%) patients had tumor size greater than 4 cm. The most frequent variants reported were microcarcinoma (n=23, 41%) and follicular variant PTC (n=20, 35.7%). Sixty-eight patients received RAI ablation therapy. Among this subset, there were four patients who were given second RAI dose to achieve ER and they remained in the same category in subsequent follow-ups. Majority of the population fell under the ATA low-risk stratification (76.92%).

Table 2 illustrates the comparison of demographic and clinical profile of patients according to response to therapy. Results showed that 21.95% (95% CI = 14.15% to 32.42%) had worsening response to therapy, while 78.05% remained to have ER (95% CI = 67.58% to 85.85%). Comparative analyses also revealed no statistical significance between those with and without worsening response to therapy ($p>0.05$). The average median stimulated and unstimulated thyroglobulin at follow-up were 0.02 (SD=0.16) and 0.16 (SD=0.37), respectively. Comparative analyses of these laboratory test results according to worsening response to therapy indicate no statistically significant differences ($p>0.05$) as well. The median years of follow-up of patients with worsening response to therapy was 7 years (IQR 3 to 11) from the time ER was documented. Among these patients, 17 (94.44%) have stage 1 disease, 14 (77.78%) were classified as ATA low risk for disease recurrence.

The patients with worsening response (n=18) as seen in Table 3 were further subdivided into IR (n=15), BR (n=1), and SR (n=2). Both patients who had developed SR had ER on first DRS, stage 1 disease, low ATA risk stratification, were both diagnosed of SR within five years after achieving ER. One of these patients had unifocal microcarcinoma not initially treated with RAI after thyroidectomy and was subsequently given 28.7 mci of RAI after developing SR.

Seventeen out of 74 patients with stage 1 disease and one out of five patients with stage 2 disease had progressed to worsening response. The remainder was not assessed for extent of disease due to undocumented histopathology report and post-therapy scan in those who received RAI. Seventy-seven percent (n=14) of patients with worsening response were ATA low-risk while 22% (n=4) were intermediate-risk (Table 4). There was no ATA high-risk patient included in this study. Of the 15 patients who developed IR, 11 patients were ATA low-risk and 13 subsequently underwent RAI therapy.

It can be noted that 5.56% (n = 1) had biochemical incomplete response (95% CI = 0.63% to 35.45%), 11.11% (n = 2) had structural incomplete response (95% CI = 2.39% to 38.91%), and 83.33% (n = 11) had IR (95% CI = 55.88% to 95.18%). Comparative analyses of the median TSH levels (χ^2 = 5.03, p = 0.357), ATA risk classification (χ^2 = 1.03, p = 1.000) and RAI ablation therapy (χ^2 = 5.08, p = 0.108) indicated that proportions were

Table 1. Characteristics of Study Population at Baseline (N = 82)

Characteristics	Mean (SD)	Frequency (*f*)	Percentage (%)
Age (Years; $\bar{x}$, SD)	47.80 (12.85)		
Age Group (f, %)			
<55 Years Old		54	65.85%
≥55 Years Old		28	34.15%
Sex (f, %)			
Male		8	4.88%
Female		78	95.12%
Family History of Thyroid Cancer (f, %)		2	2.44%
Family History of Goiter (f, %)		22	26.83%
Histologic Tissue Subtype of PTC (f, %; N = 56)			
Conventional		10	17.86%
Tall Cell		1	1.79%
Follicular		20	35.71%
Microcarcinoma		23	41.07%
Others		2	3.57%
Tumor Size (f, %; N = 77)			
<2 Centimeters		50	64.94%
2 to 4 Centimeters		22	28.57%
>4 Centimeters		5	6.49%
Bilaterality (N = 77)			
Unilateral		44	74.58%
Bilateral		15	25.42%
Focality (N = 77)			
Unifocal		37	62.71%
Multifocal		22	37.29%
RAI Ablation Therapy (f, %; N = 82)			
No		14	16.05%
Yes		68	83.95%
ATA Risk Stratification (f, %; N = 78)			
Low Risk		60	76.92%
Intermediate Risk		18	23.08%
High Risk		0	0.00%

not statistically different according to the type of worsening response to therapy.

As presented in Table 5, 72.22% (n = 13) took less than 5 years (13-57 months) to develop worsening response (95% CI = 45.34% to 89.07%), while 27.78% (n = 5) took ≥5 years before the development of worsening response (95% CI = 10.93% to 54.66%). After logistic regression analysis, there was no significant association between the variables analyzed and progression to worsening response.

DISCUSSION

Mendoza, et al., described the predictors of incomplete response to therapy of Filipino patients with PTC observed in the first two years after initial treatment. They have concluded that male sex, extrathyroidal involvement and multifocality of nodules with concurrent foci of >1 cm proved to be significantly associated with incomplete response to therapy.[12] Other risk factors for disease recurrence identified in one study in China were high levels of

Table 2. Clinical Profile of Patients Who Remained Excellent Response Versus Those Who Developed Worsening Response to Therapy (N = 82)

Characteristics	Patients who achieved excellent response (N = 82)		*p*-value (Two-Tailed)
	Remained Excellent Response (n = 64; 78.05%)	With Worsening Response (n = 18; 21.95%)	
Age (Years; $\bar{x}$, SD)	48.13 (12.89)	46.67 (13.01)	0.673
Age Group (f, %)			1.000
<55 Years Old	42 (65.63%)	12 (65.63%)	
≥55 Years Old	22 (34.38%)	6 (33.33%)	
Sex (f, %)			0.571
Male	4 (6.25%)	0 (0.00%)	
Female	60 (93.75%)	18 (100.00%)	
Family History of Thyroid Cancer (f, %)	0 (0.00%)	2 (11.11%)	0.046
Family History of Goiter (f, %)	15 (23.44%)	7 (38.89%)	0.232
Histologic Tissue Subtype of PTC (f, %; N = 56)			
Conventional	8 (17.78%)	2 (18.18%)	0.969
Tall Cell	1 (2.22%)	0 (0.00%)	0.524
Follicular	17 (37.78%)	3 (27.27%)	0.410
Microcarcinoma	17 (37.78%)	6 (54.55%)	0.202
Others	2 (4.44%)	0 (0.00%)	0.363
Tumor Size (f, %; N = 77)			0.677
<2 Centimeters	37 (62.71%)	13 (72.22%)	
2 to 4 Centimeters	17 (28.81%)	5 (27.78%)	
>4 Centimeters	5 (8.47%)	0 (0.00%)	
Bilaterality (n=77)			1.000
Unilateral	44 (74.58%)	13 (72.22%)	
Bilateral	15 (25.42%)	5 (27.78%)	
Focality (n=77)			1.000
Unifocal	37 (62.71)	11 (61.11)	
Multifocal	22 (37.29)	7 (38.89)	
RAI Ablation Therapy (f, %; N = 82)			0.471
No	10 (15.63%)	4 (22.22%)	
Yes	54 (84.37%)	14 (77.78%)	
ATA Risk Stratification (f, %; N = 78)			1.000
Low Risk	46 (76.67%)	14 (77.78%)	
Intermediate Risk	14 (23.33%)	4 (22.22%)	
High Risk	0 (0.00%)	0 (0.00%)	
Median TSH Levels			0.620
<0.10	7 (10.94%)	2 (11.11%)	
0.10 to 0.50	20 (31.25%)	7 (38.89%)	
0.51 to 2.00	30 (46.88%)	9 (50.00%)	
>2.00	7 (10.94%)	0 (0.00%)	

Table 2. Clinical Profile of Patients Who Remained Excellent Response Versus Those Who Developed Worsening Response to Therapy (N = 82)

Characteristics	Patients who achieved excellent response (N = 82)		*p*-value (Two-Tailed)
	Remained Excellent Response (n = 64; 78.05%)	With Worsening Response (n = 18; 21.95%)	
Stimulated Thyroglobulin at Initial Excellent Response (N = 62)			1.000
<0.50	35 (72.92%)	10 (71.43%)	
0.50 to 1.00	13 (27.08%)	4 (28.57%)	
Unstimulated Thyroglobulin at Initial Excellent Response (N = 13)			1.000
<0.10	4 (44.44%)	1 (25.00%)	
0.10 to 0.20	5 (55.56%)	3 (75.00%)	
Median Stimulated Thyroglobulin on Follow-up			1.000
<0.50	62 (96.88%)	18 (100.00%)	
0.50 to 1.00	2 (3.13%)	0 (0.00%)	
Median Unstimulated Thyroglobulin on Follow-up			0.061
<0.10	51 (79.69%)	18 (100.00%)	
0.10 to 0.20	13 (20.31%)	0 (0.00%)	

*Significant at 0.05
†Significant at 0.01

Table 3. Type of Worsening Response (n=18)

	Frequency (%)
Biochemical Incomplete Recurrence	1 (5.56)
Structural Incomplete Recurrence	2 (11.11)
Indeterminate Response	15 (83.33)

TSH (cut-off value of 2.615 uIU/mL), tumor size, lymph node metastasis and *BRAF* V600E mutation.[20] The female predominance (95.12%) of PTC reported in majority of the studies had also been observed in this study, but the association of previously identified risk factors to worsening response were not seen in this particular population which was probably largely affected by the small sample size, low percentage of male sex and high percentage of low-risk disease patients that were included. In 2016, Sturniolo et. al examined the influence of hormonal factors on the etiology of thyroid diseases given that DTC is three times more common in women than in men. They, including most groups that explored the same hypothesis, have concluded that estrogen receptor signaling plays a role in the development of DTC. [17,18] Despite having been previously identified as a risk factor for disease recurrence in some studies, a family history of thyroid cancer was found to be associated with ER to therapy likely due to more vigilant monitoring within the family members and therefore earlier diagnosis and treatment. [8] Other variables such as tumor size, histopathologic variant, RAI ablation therapy, ATA risk stratification and median TSH levels did not show significant correlation as well.

Based on available local and international data, however, Filipinos are found to be at a higher risk to develop disease recurrence compared to non-Filipino patients with PTC.[5] In our study, we noted that majority of those who have ER at the outset (n=59, 74.6%) remained to have ER (n=48/59, 81.3%) up to the latest documented follow-up. According to the study done by Tuttle, et al., those who have ER had a 1%-4% chance of developing disease recurrence.[16] From this, we can infer that achieving ER at the first DRS might be correlated with better long-term outcomes if done in a larger sample size. In contrast to 15 (18.99%) patients that had an initial DRS of IR, 6 (40%) of these patients had eventually developed worsening response to therapy. It was also worth mentioning that Albano, et

Table 4. Association of Median TSH Levels, ATA Risk Classification and RAI Ablation Therapy with the Type of Worsening Response (N = 18)

Characteristics	Type of Worsening Response to Therapy (N = 18)				p-value (Two-Tailed)
	Biochemical Recurrence (n = 1; 5.56%)	Structural Recurrence (n = 2; 11.11%)	Indeterminate Response (n = 15; 83.33%)	Total (N = 18)	
Median TSH Levels					0.357
<0.10	0 (0.00%)	1 (50.00%)	1 (6.67%)	2 (11.11%)	
0.10 to 0.50	0 (0.00%)	0 (0.00%)	7 (46.67%)	7 (38.89%)	
0.51 to 2.00	1 (100.00%)	1 (50.00%)	7 (46.67%)	9 (50.00%)	
>2.00	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
ATA Risk Stratification					1.000
Low Risk	1 (100.00%)	2 (100.00%)	11 (73.33%)	14 (77.78%)	
Intermediate Risk	0 (0.00%)	0 (0.00%)	4 (26.67%)	4 (22.22%)	
High Risk	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
RAI Ablation Therapy					0.108
Without RAI Ablation Therapy	1 (100.00%)	1 (50.00%)	2 (13.33%)	4 (22.22%)	
With RAI Ablation Therapy	0 (0.00%)	1 (50.00%)	13 (86.67%)	14 (77.78%)	

* Significant at 0.05
† Significant at 0.01

al., further emphasized that the risk of patients with IR developing into structural persistent or recurrent disease was associated more with elevated Tg levels than elevated anti-Tg levels and imaging-positive subgroups during serial DRS.[11]

A study done in PGH had concluded that RAI therapy was a significant protective factor against disease recurrence among low-risk PTC patients.[4] Despite this, there was no evidence that delayed discovery and treatment of persistent disease of those who did not undergo RAI therapy might decrease the chance of cure in these patients.[7] In comparison with our study, 14 out of 18 patients with worsening response underwent prior RAI ablation therapy, wherein 13 out of 14 patients developed IR and 1 out of 14 developed SR (Table 3). This might be further correlated to the extent of initial tumor and probably surgical-related factors like the degree of residual thyroid tissues, or in some studies, aggravated by inadequate TSH suppression during follow-up.[20]

After initial management with total thyroidectomy and/or RAI therapy, patients were recommended to be monitored biochemically and through imaging studies to detect biochemical or structural persistence and recurrence of disease, with frequency of monitoring largely dependent on ATA risk stratification at the time of diagnosis. Serum thyroglobulin with anti-thyroglobulin in low- to intermediate-risk patients should be monitored every 6-12 months from the time of diagnosis. Once they have achieved ER to therapy, a less stringent monitoring may be utilized. [7] TSH suppression therapy during follow-up had been shown to improve disease recurrence, progression and mortality. The recommended initial TSH targets for low-, intermediate- and high-risk patients are 0.5-2 uIU/mL, 0.1-0.5 uIU/mL and <0.1 uIU/mL respectively, taking into consideration other pre-existing conditions of the patient such as age >60 years old, presence of heart disease and osteoporosis. In this study, the TSH levels during follow-up of both groups (those who remained ER and with worsening response) were between the median TSH values of 0.10-2.00 uIU/mL. No significant association between median TSH levels and worsening response was observed.

Durante, et al., reported that half of PTC recurrences can occur within the first three years and up to more than 75% within the first five years.[19] The median time duration of follow-up of patients with worsening response in this study was eight point five years from the time of diagnosis and seven years from the time ER was documented. Thirteen out of 18 patients developed worsening response

Table 5. Time Duration to Worsening Response to Therapy (N = 18)

Characteristics	Time to Worsening Response to Therapy (N = 18)		p-value (Two-Tailed)
	<5 Years (n = 13; 72.22%)	≥5 Years (n = 5; 27.78%)	
Age (Years; $\bar{x}$, SD)	47.46 (13.19)	44.60 (13.79)	0.689
Age Group (*f*, %)			0.615
<55 Years Old	8 (61.54%)	4 (80.00%)	
≥55 Years Old	5 (38.46%)	1 (20.00%)	
Sex (*f*, %)			–
Male	0 (0.00%)	0 (0.00%)	
Female	13 (100.00%)	5 (100.00%)	
Histologic Tissue Subtype of PTC (f, %; N = 56)			
Conventional	1 (12.50%)	1 (33.33%)	0.306
Tall Cell	0 (25.00%)	0 (0.00%)	0.217
Follicular	2 (25.00%)	1 (33.33%)	0.722
Microcarcinoma	5 (62.50%)	1 (33.33%)	0.266
Others	0 (0.00%)	0 (0.00%)	–
Tumor Size (*f*, %; N = 77)			1.000
<2 Centimeters	9 (69.23%)	4 (80.00%)	
2 to 4 Centimeters	4 (30.77%)	1 (20.00%)	
>4 Centimeters	0 (0.00%)	0 (0.00%)	
RAI Ablation Therapy (*f*, %; N = 81)			0.278
No	4 (30.77%)	0 (0.00%)	
Yes	9 (69.23%)	5 (100.00%)	
Initial Dynamic Risk Assessment (f, %; N = 78)			0.711
Excellent Response	7 (53.85%)	4 (80.00%)	
Biochemical Incomplete	0 (0.00%)	0 (0.00%)	
Structural Incomplete	1 (7.69%)	0 (0.00%)	
Indeterminate	5 (38.46%)	1 (20.00%)	
Median TSH Levels			1.000
<0.10	2 (15.38%)	0 (0.00%)	
0.10 to 0.50	5 (38.46%)	2 (40.00%)	
0.51 to 2.00	6 (46.15%)	3 (60.00%)	
>2.00	0 (0.00%)	0 (0.00%)	
Stimulated Thyroglobulin at Initial Excellent Response (N = 62)			1.000
<0.50	6 (66.67%)	4 (80.00%)	
0.50 to 1.00	3 (33.33%)	1 (20.00%)	
Unstimulated Thyroglobulin at Initial Excellent Response (N = 13)			–
<0.10	1 (25.00%)	0 (0.00%)	
0.10 to 0.20	3 (75.00%)	0 (0.00%)	
Median Stimulated Thyroglobulin on Follow-up			–
<0.50	13 (100.00%)	5 (100.00%)	
0.50 to 1.00	0 (0.00%)	0 (0.00%)	
Median Unstimulated Thyroglobulin on Follow-up			–
<0.10	13 (100.00%)	5 (100.00%)	
0.10 to 0.20	0 (0.00%)	0 (0.00%)	

* Significant at 0.05
† Significant at 0.01

within five years while the remaining five patients documented worsening response more than five years from the time of ER.

It is important to underscore the role of genetic factors to poorer outcomes. A study in Hawaii found that Filipinos have a high preponderance of the BRAF mutation (83.8% vs 45%) when compared to the norm in literature.[13] This was supported by local data which explored genetic mutation in Filipinos with PTC, specifically BRAF V600E mutation, as a contributory factor that had been linked to a more aggressive phenotype of PTC in terms of extrathyroidal extension. No statistical significance was determined in their study due to small sample size.[14]

CONCLUSION

In conclusion, no significant differences were found between worsening response and patient variables such as age, sex, family history of goiter, histologic tissue subtype, tumor size, focality, ATA risk stratification, median TSH levels and history of RAI therapy. Majority of the worsening responses were documented in the first five years after surgery as was seen in most studies. We recommend a similar single or multicenter retrospective study with a larger population with more uniform and longer follow-up duration to more accurately identify the determinants of worsening response in the Filipino population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL CONSIDERATIONS

This research protocol was submitted to the UST Hospital Research Ethics Committee (REC). This had already been reviewed and approved by our section's Technical Review Board (TRB) and since this only involved chart review, a waiver for consent was requested and was approved.

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