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Risk Factors Associated with Disease Recurrence among Patients with Low-Risk Papillary Thyroid Cancer Treated at the University of the Philippines-Philippine General Hospital

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Background: The management of papillary thyroid carcinoma (PTC) in high-risk patients is well-standardized. However, this is not the case for low-risk patients. Filipinos show a high incidence of recurrence of thyroid cancer. Thus, the identification of risk factors for recurrence in this population could potentially identify individuals for whom radioactive iodine (RAI) therapy might be beneficial.

Methods: We reviewed the medical records of adult Filipinos with low-risk PTC who underwent near-total or total thyroidectomy at the University of the Philippines-Philippine General Hospital. Multivariate logistic regression analysis was used to determine risk factors for recurrence.

Results: Recurrence was documented in 51/145 of patients (35.17%) included in this study. Possible risk factors such as age, sex, family history, smoking history, tumor size, multifocality, prophylactic lymph node dissection, initial thyroglobulin (Tg) level, initial anti-thyroglobulin (anti-Tg) antibody concentration, suppression of thyroid stimulating hormone production, and RAI therapy were analyzed. Multivariate analysis revealed that a tumor diameter 2 to 4 cm (odds ratio [OR], 9.17; 95% confidence interval [CI], 1.62 to 51.88; P=0.012), a tumor diameter >4 cm (OR, 16.46; 95% CI, 1.14 to 237.31; P=0.04), and a family history of PTC (OR, 67.27; 95% CI, 2.03 to 2228.96; P=0.018) were significant predictors of recurrence. In addition, RAI therapy (OR, 0.026; 95% CI, 0.01 to 0.023; P≤0.005), an initial Tg level ≤2 ng/mL (OR, 0.049; 95% CI, 0.01 to 0.23; P≤0.005), and an anti-Tg antibody level ≤50 U/mL (OR, 0.087; 95% CI, 0.011 to 0.67; P=0.019) were significant protective factors.

Conclusion: A tumor diameter ≥2 cm and a family history of PTC are significant predictors of recurrence. RAI therapy and low initial titers of Tg and anti-Tg antibody are significant protective factors against disease recurrence among low-risk PTC patients.

Keywords: Thyroid neoplasms; Thyroid cancer, papillary; Recurrence

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INTRODUCTION

Thyroid carcinoma is the most common endocrine malignancy and it has increased 2- to 4-fold in incidence over the past decade. Well-differentiated thyroid cancer, of either the papillary or follicular type, is the most common form, making up 90% of all thyroid malignancies [1,2].

Among patients with papillary thyroid carcinoma (PTC), those stratified as low-risk make up 80% of cases [3]. Management of patients with PTC includes thyroidectomy with or without RAI therapy. The treatment strategy is well-established and has been proven to successfully enhance the outcomes and prognoses of most patients [4,5]. However, recommendations for the management of low-risk thyroid cancer patients have been contradictory [4,5]. Currently, our local Philippine guidelines state that certain low-risk patients may not be receive RAI therapy [5]. Although such patients generally have good prognoses, recurrence develops in up to 13% of them [6,7].

The well-established risk factors for disease recurrence include age >45 years, a family history of PTC, being male, multifocality, nodal involvement at the time of presentation, and having tumors >4 cm. Recent studies have also shown that never-smoking status reduces the risk of thyroid cancer (risk ratio [RR], 0.71; 95% confidence interval [CI], 0.60 to 0.83) [5,8]. Soyluk et al. [9] showed that low- to intermediate-risk PTC patients were at an increased risk of recurrence if their initial post-ablative thyroglobulin (Tg) level in serum was ≥0.3 ng/mL or if they were positive for anti-thyroglobulin (anti-Tg) antibody. There are currently no international or local data on factors affecting disease recurrence among low-risk PTC patients.

The prognosis of PTC is optimal when the diagnosis, staging, treatment, and the risk of recurrence are timely and carefully managed. As disease-specific mortality is low (1%), the most relevant oncological outcome is disease recurrence [9,10]. As most patients present with low-risk disease, the development of measures predicting the risk of recurrence in this subgroup is warranted. We identified predictors of disease recurrence among Filipinos with low-risk PTC. Our results can be used to further individualize treatment plans, avoid unnecessary costs, and improve quality of life.

METHODS

Study design

This was a retrospective cohort study of patients diagnosed with low-risk PTC treated at the thyroid outpatient clinic of the University of the Philippines-Philippine General Hospital (UP-PGH). This tertiary hospital is the National University Hospital of the Philippines.

Inclusion criteria

Adult patients (≥19 years of age at the time of diagnosis) diagnosed with PTC after near-total or total thyroidectomy, who developed recurrence at any time or who underwent at least 5 years of follow-up without recurrence, and who were classified as low-risk based on the American Thyroid Association (ATA) 2009 guidelines were enrolled. The low-risk classification is based on the following: absence of local or distant metastases, resection of all macroscopic tumors, absence of tumor invasion of locoregional tissues, absence of aggressive tumor histology (tall cells, insular cells, columnar cells) or vascular invasion, and uptake of ^{131}I (if given) limited to the thyroid bed on the first post-treatment whole-body radioactive iodine (RAI) scan.

Exclusion criteria

Patients for whom data were lacking in terms of either initial Tg or anti-Tg antibody levels or post-therapy whole-body scans were excluded.

Chart retrieval

The outpatient charts of all patients who met the inclusion criteria were retrieved from the UP-PGH medical records section and from the database of the Section of Endocrinology. Charts that were in active circulation, thus both available and retrievable, were included.

Data collection

Age at diagnosis, sex, any family history of thyroid cancer, smoking history, date of surgery, tumor size, prescription (or not) of post-surgical RAI therapy, initial post-ablative and post-surgical Tg and anti-Tg antibody levels in serum, and the extent of thyroid stimulating hormone (TSH) suppression were all descriptively documented (means, standard deviations, percentages). Then these variables were analyzed to determine if they constituted risk factors for disease recurrence.

Recurrent or distant metastatic disease was defined as disease developing >6 months after total thyroidectomy, with or without RAI treatment. Locoregional recurrence was defined (as by the ATA) as cervical/superior mediastinal disease identified on imaging and ideally proven by biopsy. Distant metastatic disease was defined as disease developing outside the neck region identified by imaging or proven by biopsy. Bio-

chemical recurrent disease was defined as elevated stimulated (>2 ng/mL) or unstimulated (>1 ng/mL) Tg levels in patients with previously undetectable Tg levels, diagnosed >6 months after total thyroidectomy with or without RAI therapy, and associated with normal anti-Tg antibody levels (≤50 U/mL). Disease recurrence was defined as recurrent or new-onset lymphadenopathy, or distant metastases proven to originate from thyroid cancer by biopsy or RAI whole-body scan [4].

The subsequent management and monitoring of low-risk patients who did not undergo RAI therapy differed from those who underwent RAI therapy. Follow-up of the former patients typically includes evaluation of TSH suppression by levothyroxine, neck ultrasonography, and measurement of recombinant human TSH (rhTSH)-stimulated Tg levels. At our institution, measurement of rhTSH-stimulated Tg levels in this group of patients is not recommended; the cost is prohibitive [4,5]. Notably, the absence of RAI therapy renders monitoring of Tg levels challenging in such patients, as remnant thyroid tissue is almost always present after surgery, rendering Tg detectable. Currently, no particular Tg level is accepted as a reliable cut-off for accurate prediction of disease recurrence. Rather, the trend in Tg level over time is monitored; increases over time are suggestive of recurrence and a need for work-up [4].

Statistical analysis

Patients were grouped into those who did or did not suffer recurrences. The baseline characteristics of the two groups were compared using Fisher exact test for qualitative variables and the two-sample *t* test for continuous quantitative variables. Then multivariate logistic regression analysis was performed to identify significant risk factors for disease recurrence. The predictive power of each variable was calculated and expressed as an odds ratio (OR) with the 95% CI. A $P \leq 0.05$ was considered to indicate statistical significance.

This study was approved by the Technical Review Board of the Department of Medicine and the University of the Philippines Manila Research Ethics Board (approval number: IRB [MED] 2015-055-01).

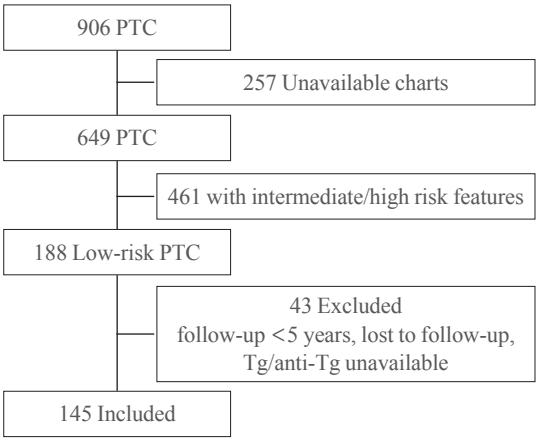

Fig. 1. Inclusion and exclusion flow chart. PTC, papillary thyroid cancer; Tg, thyroglobulin; Anti-Tg, anti-thyroglobulin.

RESULTS

A total of 906 PTC patients were listed in the outpatient database; 649 charts (72%) were available for review, and 188 patients (29%) were considered low-risk. Of these, 145 patients fulfilled the inclusion criteria and were included in the study (Fig. 1).

The mean age at diagnosis of the 145 low-risk PTC patients was 39.74±10.67 years; 5 (10.34%) were males. Most patients had no family history of thyroid cancer and were non-smokers. Prophylactic lymph node (LN) dissection was performed in five patients (3.45%). The mean tumor diameter was 2.29±1.37 cm. Multifocality was evident in 25 patients (17.24%). Ninety-two patients (63.45%) underwent RAI therapy after thyroidectomy, at a median interval of 8±9.69 months after surgery. Ninety-four patients (64.83%) had initial Tg levels ≤2 ng/mL. A total of 128 patients (88.27%) had initial anti-Tg an-

Table 1. Demographic and Clinical Characteristics of Filipino Patients with Low-Risk Papillary Thyroid Cancer (*n*=145)

Characteristic	Value
Age at diagnosis, yr	39.74±10.67
Male sex	15 (10.34)
Family history	2 (1.38)
Smoking history	9 (6.21)
Prophylactic LN dissection	5 (3.45)
Tumor diameter, cm	2.29±1.37
Multifocality	25 (17.24)
RAI therapy given	92 (63.45)
Time to initial RAI from surgery, mo	8±9.69
Initial Tg level, ≤2 ng/mL	94 (64.83)
Initial anti-Tg antibody level, ≤50 U/mL	128 (88.27)
Extent of TSH suppression, ≤0.27 mU/L	100 (68.97)
Follow-up duration, mo	112.28±63.03

Values are expressed as mean±SD or number (%).
LN, lymph node; RAI, radioactive iodine; Tg, thyroglobulin; Anti-Tg, anti-thyroglobulin; TSH, thyroid-stimulating hormone.

Table 2. Comparison of Baseline Characteristics among Patients Who Did and Did Not Undergo RAI

Variable	With RAI (*n*=92)	Without RAI (*n*=53)	*P* value
Age at diagnosis, yr	39±9.18	39±12.94	0.871
Male sex	9 (9.78)	6 (11.32)	0.783
Family history of PTC	2 (2.17)	0	0.533
Smoking history	5 (5.43)	4 (7.55)	0.724
Prophylactic LN dissection	4 (4.35)	1 (1.89)	0.653
Tumor diameter, cm	2.33±1.39	2.23±1.36	0.967
<2	38 (41.3)	21 (39.62)	
2–4	45 (48.9)	27 (50.9)	
>4	9 (9.8)	5 (9.43)	
Multifocality	17 (18.48)	8 (15.1)	0.655
Initial Tg level, ≤2 ng/mL	85 (92.4)	9 (16.98)	<0.005
Initial anti-Tg antibody level, ≤50 U/mL	84 (91.3)	44 (83.02)	0.18
TSH suppression, ≤0.27 mU/L	76 (82.61)	24 (45.28)	<0.005
Follow-up duration, mo	113±53.39	109±77.47	0.702
Recurrence	7 (7.61)	44 (83.02)	<0.005
Locoregional	7 (7.61)	35 (66.04)	<0.005
Distant	0	9 (16.98)	<0.005

Values are expressed as mean±SD or number (%).
RAI, radioactive iodine; PTC, papillary thyroid carcinoma; LN, lymph node; Tg, thyroglobulin; anti-Tg antibody, anti-thyroglobulin antibody; TSH, thyroid-stimulating hormone.

Table 3. Univariate Logistic Regression Analysis of Risk Factors for Disease Recurrence among Patients with Low-Risk Papillary Thyroid Cancer

Variable	With recurrence (*n*=51)	Without recurrence (*n*=94)	Relative risk	*P* value (95% CI)
Age at diagnosis, yr	38.98±12.66	40.15±9.46	0.99	0.528 (0.95–1.02)
Male sex	6 (11.76)	9 (9.57)	1.26	0.68 (0.42–3.76)
Family history of PTC	1 (1.96)	1 (1.06)	1.86	0.663 (0.11–30.37)
Smoking history	4 (7.84)	5 (5.32)	1.51	0.550 (0.39–5.91)
Prophylactic LN dissection	2 (3.92)	3 (3.19)	1.24	0.818 (0.20–7.66)
Tumor diameter, cm	2.59±1.32	2.13±1.38		
<2	14 (27.45)	45 (47.87)	2.43	
2–4	31 (60.8)	41 (43.62)	2.41	0.022 (1.14–5.19)
>4	6 (11.76)	8 (8.51)		0.156 (0.71–8.14)
Multifocality	8 (15.69)	17 (18.08)	0.843	0.715 (0.34–2.11)
Initial Tg level, ≤2 ng/mL	8 (15.7)	86 (91.5)	0.017	<0.005 (0.01–0.049)
Initial anti-Tg antibody level, ≤50 U/mL	41 (80.39)	87 (92.55)	0.329	0.036 (0.117–0.93)
TSH suppression, ≤0.27 mU/L	22 (43.14)	78 (82.98)	0.16	<0.005 (0.07–0.34)
RAI therapy	7 (13.73)	85 (90.43)	0.02	<0.005 (0.01–0.05)

Values are expressed as mean±SD or number (%).
CI, confidence interval; PTC, papillary thyroid carcinoma; LN, lymph node; Tg, thyroglobulin; anti-Tg, anti-thyroglobulin; TSH, thyroid-stimulating hormone; RAI, radioactive iodine.

tibody levels ≤50 U/mL, and 100 patients (68.97%) exhibited adequate TSH suppression (≤0.27 mU/L). The mean follow-up duration was 112.28±63.03 months from diagnosis. Disease recurrence was noted in 51 patients (35.17%) at a median

Table 4. Multivariate Logistic Regression Analysis of Risk Factors for Recurrence in Filipinos with Low-Risk Papillary Thyroid Cancer

Significant risk factor	Relative risk	*P* value (95% CI)
Tumor diameter, cm		
2–4	9.17	0.012 (1.62–51.88)
>4	16.46	0.04 (1.14–237.31)
Family history of PTC	67.27	0.018 (2.03–2,228.96)
RAI therapy	0.026	<0.005 (0.01–0.023)
Initial Tg level, ≤2 ng/mL	0.049	<0.005 (0.01–0.23)
Initial anti-Tg antibody level, ≤50 U/mL	0.087	0.019 (0.011–0.67)

CI, confidence interval; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; Tg, thyroglobulin; anti-Tg, anti-thyroglobulin.

interval of 60±65.28 months after thyroidectomy (Table 1).

Demographic and clinical characteristics did not differ significantly between the two groups in terms of mean age at diagnosis, the proportion of males, a family history of thyroid cancer, smoking history, prophylactic LN dissection, tumor size, multifocality, initial anti-Tg antibody level, or follow-up duration. The initial Tg level, the extent of TSH suppression, and the frequency of recurrence did differ significantly. More patients in the RAI group had Tg levels ≤2 ng/mL, adequate TSH suppression, and less disease recurrence (Table 2).

Univariate logistic regression showed that a tumor diameter 2 to 4 cm (OR, 2.43; 95% CI, 1.14 to 5.19; P=0.022) predicted disease recurrence. An initial Tg level ≤2 ng/mL (OR, 0.017; 95% CI, 0.01 to 0.049; P≤0.005), initial anti-Tg antibody-positivity (OR, 0.329; 95% CI, 0.117 to 0.93; P=0.036), adequate TSH suppression, and RAI therapy significantly protected against disease recurrence among low-risk PTC patients: TSH suppression (OR, 0.16; 95% CI, 0.07 to 0.34; P≤0.005) and RAI vs. no RAI (OR, 0.02; 95% CI, 0.01 to 0.05; P≤0.005) (Table 3).

Multivariate logistic regression analysis of all risk factors revealed that a tumor diameter 2 to 4 cm (OR, 9.17; 95% CI, 1.62 to 51.88; P=0.012) or >4 cm (OR, 16.46; 95% CI, 1.14 to 237.31; P=0.04) and a family history of PTC (OR, 67.27; 95% CI, 2.03 to 2,228.96; P=0.018) were significant predictors of disease recurrence. RAI therapy (OR, 0.01; 95% CI, 0.001 to 0.033; P≤0.005), an initial Tg level ≤2 ng/mL (OR, 0.049; 95% CI, 0.01 to 0.23; P≤0.005), and an initial anti-Tg antibody level ≤50 U/mL (OR, 0.087; 95% CI, 0.011 to 0.67; P=0.019) significantly protected against disease recurrence (Table 4).

DISCUSSION

The incidence of disease recurrence in our cohort of low-risk PTC patients was 35.17%, thus higher than noted in other reports (up to 13%) [6,7]. This may be attributable to the higher incidence of disease and higher risk of recurrence among Filipinos. The age-adjusted incidence rate of PTC in Filipinas (females) is more than double that of Japanese females [11], and Filipinos (male or female) are at significantly higher risk of thyroid cancer recurrence than non-Filipino patients [12]. In addition, the definition of "low-risk PTC" may vary among reports, rendering comparisons difficult. We used the criteria proposed by the 2009 ATA guidelines to define low-risk PTC.

A comparison of the groups who received and did not receive RAI therapy revealed significant differences in initial Tg levels, attainment of adequate TSH suppression, and disease recurrence. The significant difference in the initial Tg level was attributable to the difference in follow-up monitoring between the groups. Patients who do not undergo RAI therapy tend to have detectable Tg levels; some remnant thyroid tissue is nearly always present after surgery. The between-group difference in TSH suppression may be explained by variation in the recommended levels of TSH suppression for the two groups. These levels are 0.1 to 0.27 mU/L and 0.1 to 0.5 mU/L for patients who have and have not undergone RAI, respectively [4,5]. Furthermore, differences in monitoring and assessment of recurrence among patients who have and have not undergone RAI therapy may be associated with detection bias. Only patients who had undergone RAI were scheduled for whole-body scans, allowing disease to be detected earlier and more frequently.

Prophylactic LN dissection is currently not recommended at our institution unless suspicious LNs are noted on routine preoperative ultrasound. This explains the low frequency of such procedures at our hospital [5].

Multivariate analysis showed that large tumor size (≥2 cm) and a family history of PTC were significant predictors of disease recurrence. These data are similar to data obtained in other countries (RR, 2.69; 95% CI, 2.06 to 3.50) [13]. RAI therapy, an initial Tg level ≤2 ng/mL, and an initial anti-Tg antibody level ≤50 U/mL were also significant predictors of disease recurrence, again consistent with foreign data [9,14]. The protective effect of RAI therapy is consistent with the results of a study on papillary thyroid microcarcinoma patients, which may also be considered to be low-risk PTC patients. Recurrence was higher among those who did not undergo RAI therapy

post-surgery (RR, 8.6; 95% CI, 4.4 to 17.1) [15]. However, most published data do not indicate that RAI therapy protects significantly against disease recurrence [16,17]. These large studies were performed on ethnic groups that did not include Filipinos, and the definition of "low-risk" differed from that which we employed in the present study. The more prevalent prescription of RAI therapy among this group is attributable to the preferences of healthcare providers which is mainly influenced by the poor patient follow-up in our setting.

We limited our study population to those with PTC, because prognoses may differ between PTC patients and those with follicular thyroid carcinoma. We thus eliminated any possible difference in disease behavior that may have contributed to the different outcomes of other studies. The major limitation of our study is the unavailability of some medical records. To further strengthen the predictive utilities of the risk factors that we have defined, work with larger cohorts is required.

In conclusion, we found that the incidence of low-risk PTC recurrence among Filipinos was 35.17%, similar to the figure reported by Kus et al. [12]. A large tumor diameter ≥2 cm and a family history of PTC were significant predictors of disease recurrence. RAI therapy, an initial Tg level ≤2 ng/mL, and an initial anti-Tg antibody level ≤50 U/mL significantly protected against disease recurrence, consistent with previously published data. We focused on patients with low-risk PTC, as defined by the ATA. Information on risk factors for disease recurrence in this group are still lacking, and reports on the benefits afforded by RAI ablative therapy are conflicting. We found that a lack of such therapy increased the incidence of recurrence, and suggest that more aggressive initial management (including RAI therapy) should be considered even for low-risk patients. In addition, tumor size should be included when assessing the risk of disease recurrence. We suggest that low-risk PTC should be redefined to include patients with tumors <2 cm in diameter, at least in the Filipino population. Our data may have important practical implications. Most cases encountered in clinical practice have low-risk PTC. The identification of risk factors for disease recurrence may help guide the provision of specific treatments tailored specifically toward low-risk PTC Filipino patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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