Radioactive Iodine Remnant Ablation and Disease Recurrence in Filipinos With Low-risk Papillary Thyroid Microcarcinoma

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Abstract

Introduction: Low-risk papillary thyroid microcarcinomas (PTMC) have an indolent course and favorable prognosis. In the Philippines, radioactive iodine (RAI) remnant ablation is frequently given to patients with low-risk PTMC because of studies showing that Filipinos have more aggressive thyroid cancers. This study aims to determine if RAI remnant ablation prevents thyroid cancer recurrence among Filipino patients with low-risk PTMC who underwent thyroidectomy at a tertiary hospital in the Philippines.

Methods: A retrospective cohort study was conducted among adult patients with low-risk PTMC who underwent total thyroidectomy from 2006 to 2016. Outcomes were classified as positive or negative for disease recurrence based on imaging results and serum thyroglobulin levels during each follow-up visit. Recurrence-free curves were estimated using Kaplan-Meier method and compared using Cox regression analysis.

Results: A total of 90 cases of low-risk PTMC were included in the analysis with a mean follow-up duration of 41.88 months (range, 12-129 months). Forty eight patients (53.33%) underwent RAI remnant ablation (RAI group) and 42 patients (46.67%) did not (No RAI group). Six patients (6.67%) had disease recurrence at a median of 18 months (range, 12-70 months). The recurrence rates in the No RAI group were 2.8% at one year and 10.84% in five years and the recurrence rates in the RAI group were 0% at one year and 9.84% at five years. (HR, 5.34; 95% CI, 0.86 to 33.02; *P*=0.07).

Conclusion: This study did not provide sufficient evidence that RAI remnant ablation prevents disease recurrence in Filipino patients with low-risk PTMC. Future randomized, prospective trials involving larger sample sizes and longer follow-up duration are necessary to confirm our findings.

Keywords: papillary thyroid micorcarcinoma, thyroid neoplasm, thyroid cancer, papillary

Introduction

Papillary thyroid microcarcinoma (PTMC) is defined by the World Health Organization as papillary thyroid carcinoma (PTC) one centimeter or less in diameter.[1] In the Philippines, the prevalence rate of PTMC is reported at 22%.[2] Mortality associated with PTMC is low with survival rates reported as high as 99% and recurrence rates as low as five percent.[3,4] The American Thyroid Association (ATA) recommends RAI remnant ablation based on the postoperative risk stratification of patients with PTC. RAI remnant ablation is not recommended for those belonging to the ATA low-risk category or stage I disease because of its low recurrence rate and disease-specific mortality. The low-risk category include those with intrathyroidal PTC (no local or distant metastases, no tumor invasion of loco-regional structures, no vascular invasion, clinical N0 or ≤5 pathologic N1 micrometastases); those with complete tumor resection; those without aggressive tumor histology and if RAI is given, has no RAI-avid metastatic foci outside the thyroid bed on the first post-treatment whole body scan (WBS).[5]

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However, studies have shown that Filipinos have greater thyroid cancer recurrence rate compared to non-Filipino ethnicities in a study by Kus et al. (25% vs 9.5%, odds ratio (OR), 3.20; 95% confidence interval (CI), 1.23-7.49; *P*=.004).[6] This is even higher in local studies that showed PTC among Filipinos having a more aggressive behavior with recurrence rate of 30-35%.[7,8] Local studies have also shown that RAI remnant ablation was protective in reducing tumor recurrence in patients with low-risk PTC.[8,9] But these studies involved patients with low-risk PTC in general.

Studies of PTMC treated with RAI remnant ablation following thyroidectomy show conflicting results. Several studies demonstrated that RAI remnant ablation following thyroidectomy in PTMC patients improved recurrence and

disease-free survival rates.[10-13] In particular a local study done by Labitag et al. involving 109 patients with PTMC showed that RAI remnant ablation after total thyroidectomy showed a trend for lower risk of persistent disease but this did not reach statistical significance (OR, 0.384; 95% CI, 0.055-2.623; *P*=0.4116).[14] On the other hand, several other studies have shown that neither mortality nor recurrence in PTMC patients was improved by RAI remnant ablation.[15-18]

Thus, the management of thyroid cancer in the Philippines remains heterogeneous. Some clinicians would still treat low-risk PTMC with RAI remnant ablation because of the aforementioned epidemiologic studies showing that Filipinos have more aggressive thyroid cancers. Local studies involved patients with low-risk PTC in general and among those with PTMC in particular, results did not reach statistical significance. This study aims to determine if RAI remnant ablation prevents thyroid cancer recurrence among Filipino patients with low-risk PTMC who underwent thyroidectomy at The Medical City (TMC).

Methods

A retrospective cohort study was conducted among adult patients with low-risk PTMC who underwent thyroidectomy at TMC from 2006 to 2016. The study protocol was approved by TMC Institutional Review Board. Patients with histopathologic diagnosis of PTMC were retrieved from the pathology section. Medical charts of identified patients were retrieved from the medical record section and/or attending consultant clinic. Inclusion criteria were as follows: 1) aged 18 years and above, 2) diagnosed case of intrathyroidal PTMC by histopathology, 3) with minimum one year of follow-up, and 4) belonged to ATA low-risk category or stage I disease. Low-risk PTMC was defined according to the 2015 ATA guidelines and included patients who underwent complete tumor resection (total thyroidectomy or subtotal with completion thyroidectomy), without local or distant metastasis at the time of diagnosis, no aggressive histology (e.g. tall cell, hobnail variant, columnar cell carcinoma), no vascular invasion on initial presentation, and if RAI was given, without RAI-avid metastatic foci outside the thyroid bed on the first post-treatment WBS. All patients who did not fulfill the inclusion criteria were excluded from the study.

Patient charts were reviewed and the following data were retrieved: patient and tumor characteristics, treatment strategies utilized, recurrence and clinical outcomes. Patient characteristics included age at diagnosis, gender, history of head and neck irradiation, associated comorbidities, family history of thyroid cancer and smoking history. Tumor characteristics included tumor size, variant, multifocality and laterality. For multifocal tumors, the diameter of the largest tumor was considered as the primary tumor size. Treatment forms included initial surgery, completion surgery, RAI remnant ablation and dose and thyroid stimulating hormone (TSH) suppression dose at last follow-up visit. Data for recurrence and clinical outcomes included were as follows: total follow-up duration, time to tumor recurrence, TSH level, serum thyroglobulin (Tg), Tg antibody levels, and imaging results (neck ultrasound, WBS, PET scan).

Patients who did not have evidence of disease on imaging with normal serum Tg levels six months after surgery were included in the analysis. Completion thyroidectomy performed within two months of the initial surgery was classified as total thyroidectomy. RAI remnant ablation was defined as RAI given within two months after surgery. The decision to perform RAI remnant ablation was based on the discretion of the attending endocrinologist. At each follow-up visit, the outcome was classified as positive or negative for disease recurrence based on imaging results and serum Tg levels. Disease recurrence was defined as disease developing six months or more after being considered disease-free following initial thyroidectomy, with or without RAI remnant ablation. Disease recurrence was considered in the presence of both structural (recurrent or new-onset lymphadenopathy and/or distant metastases identified by imaging or proven by biopsy) and biochemical recurrence (elevated stimulated (≥10 ng/mL) or unstimulated (≥1 ng/mL) serum Tg levels in patients with previously undetectable Tg levels.

Patients were divided into two groups, those who underwent RAI remnant ablation (RAI group) and those who did not undergo RAI remnant ablation (No RAI group). Quantitative variables were summarized as means and standard deviations. Qualitative variables were summarized as frequencies and percentages. Comparison of baseline characteristics between the two groups were analyzed using independent t-test for quantitative variables and Fisher's exact test for qualitative variables. Recurrence-free curves were estimated using Kaplan–Meier method and compared using Cox regression analysis. The level of significance was set at five percent.

Results

A flow chart of the selection of the study population is shown in Figure 1. A total of 1,422 cases of thyroidectomies were done from 2006 to 2016. Out of these, 569 (40.01%) were malignant and the rest were benign. One hundred seventy cases of PTMC (29.88%) were identified. Twenty nine cases were excluded due to the following: one had distant metastasis, 24 had extrathyroidal extension and/or lymph node metastasis, and four underwent only subtotal thyroidectomy. Among the 141 cases of PTMC who fulfilled the inclusion criteria, 31 cases were lost to follow-up and 16 cases had incomplete data for chart review, hence were excluded. A total of 90 cases of low-risk PTMC were included in the analysis. The sample size exceeded the minimum

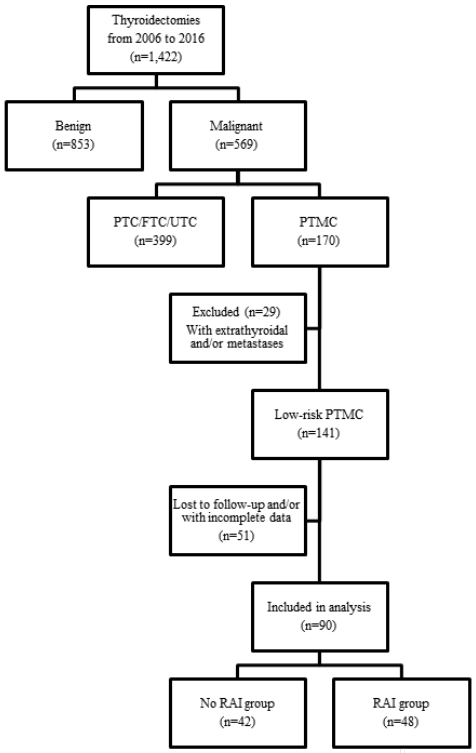

Figure 1. Flow chart of selection of the study population

requirement for the study given the desired probability level of five percent and statistical power of 90%.

The mean follow-up duration for all patients with low-risk PTMC was 41.88 months (range, 12-129 months). Among the 90 patients, 82 (91.11%) were females and eight (8.89%) were males. The mean age was 48.53±11.72 years and 64% were 45 years and older at the time of diagnosis. The mean tumor size was 0.49±0.35 cm and most patients (58.89%) had tumors ≤0.5 cm. Fifty nine patients (65.56%) had unifocal tumors and 31 patients (34.44%) had multifocal tumors. Twenty-four patients (26.67%) had bilateral tumors. The most common tumor variant was classical (52.22%) followed by follicular (31.11%). All patients received TSH suppression by levothyroxine with mean dose of 113.99±27.25 mcg/day and mean TSH level of 0.30±0.26 uIU/mL.

In our cohort, 48 patients (53.33%) underwent RAI remnant ablation (RAI group) with mean follow-up duration of 51.15 months (range, 12-129 months) and mean RAI dose of 94.33±22.56 mCi. Forty-two patients (46.67%) did not undergo RAI remnant ablation (No RAI group) with mean follow-up duration of 31.29 months (range, 12 to 114 months). Baseline characteristics of patients in both groups are shown in Table I.

The two groups were comparable at baseline except for tumor size, wherein patients in the RAI group had larger tumors compared to patients in the No RAI group (0.58±0.39 cm and 0.38±0.27 cm respectively, *p*=0.01). The estimated

Table I. Baseline characteristics of patients with low-risk PTMC

	RAI group n=48	No RAI group n=42	*p*-value
Age at diagnosis, yr, mean ± SD	48.75±11.08	48.29±12.54	0.85
Gender (%) Male Female	 6 (12.50) 42 (87.50)	 2 (4.76) 40 (95.24)	0.28
History of head/neck irradiation (%)	0	2 (4.76)	0.25
Diabetes (%)	14 (29.17)	10 (23.81)	0.21
Hypertension (%)	21 (43.75)	18 (42.86)	1.00
Family history (%) Papillary thyroid carcinoma Goiter	 2 (4.17) 12 (25)	 3 (7.14) 8 (19.05)	 0.66 0.61
Smoking history (%)	7 (14.58)	3 (7.14)	0.33
TSH, uIU/mL, mean ± SD	0.27 ± 0.27	0.34 ± 0.25	0.24
Tumor size, cm, mean ± SD	0.58 ± 0.39	0.38 ± 0.27	0.01
Tumor variant (%) Classical variant Follicular variant Sclerosing variant Oncocytic variant Mixed variants	 27 (56.25) 12 (25) 3 (6.25) 0 6 (12.5)	 20 (47.62) 16 (38.10) 1 (2.38) 1 (2.38) 4 (9.52)	0.47
Multifocality (%) Unifocal Multifocal	 27 (56.25) 21 (43.75)	 32 (76.19) 10 (23.81)	0.08
Laterality (%) Right Left Isthmus Bilateral	 14 (29.17) 15 (31.25) 3 (6.25) 16 (33.33)	 16 (38.10) 12 (28.57) 6 (14.29) 8 (19.05)	0.30
Surgery total thyroidectomy (%) Subtotal with completion thyroidectomy (%)	46 (95.83) 2 (4.17)	40 (95.24) 2 (4.76)	1.00
TSH suppression dose, mcg/d, mean ± SD	116.54±23.03	111.07±31.43	0.35

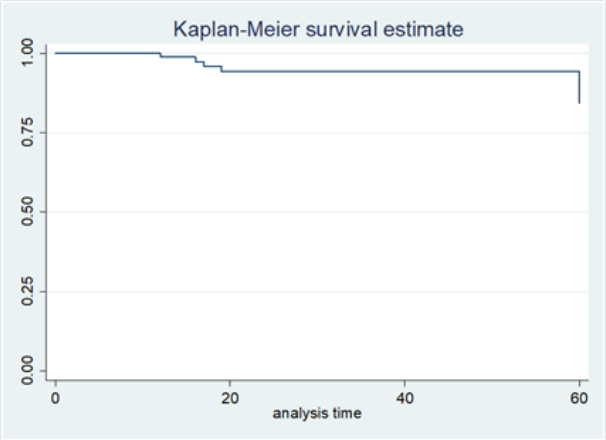

Figure 2. Kaplan-Meier estimate of recurrence rate in all low-risk PTMC patients

recurrence rate for the whole cohort was 1.25% at one year and 6.02% at two and five years (Figure 2).

In the RAI group, the estimated recurrence rate was zero percent at one year, 2.63% at two years and 9.84% at five years. In the No RAI group, the estimated recurrence rate was 2.8% at one year, 10.84% at two and five years. Based

on a Cox regression model, the recurrence rate in the No RAI group was almost five times faster than the RAI group, but this was not statistically significant (hazard ratio (HR), 4.99; 95% confidence interval (CI), 0.80 to 31.28; *P*=0.09). Controlling for the effect of tumor size, the hazard ratio for recurrence in the No RAI group was even higher than the RAI group, but this was still not statistically significant (HR, 5.34; 95% CI, 0.86 to 33.02; *P*=0.07, Figure 3).

Disease recurrence after initial therapy occurred in six patients (6.67%) at a median of 18 months (range, 12-70 months). The characteristics of patients with disease recurrence are summarized in Table II.

Among the six patients with disease recurrence, two patients underwent RAI remnant ablation and four patients did not. Five of these patients were 45 years and older at the time of diagnosis. The mean tumor size was 0.55±0.43 cm and only one patient had multifocal tumors. Four patients had tumor sizes more than 0.5 cm. Three patients had tumors with follicular variant and the rest were classical, sclerosing or oncocytic variants. Among all patients with low-risk PTMC, two patients had previously received RAI for hyperthyroidism and both of these patients had disease recurrence. Disease recurrences were identified through imaging (neck ultrasound and/or WBS) results and elevated serum Tg levels. All recurrences were localized to the thyroid bed or regional neck nodes, and none of these patients developed distant metastases during follow-up.

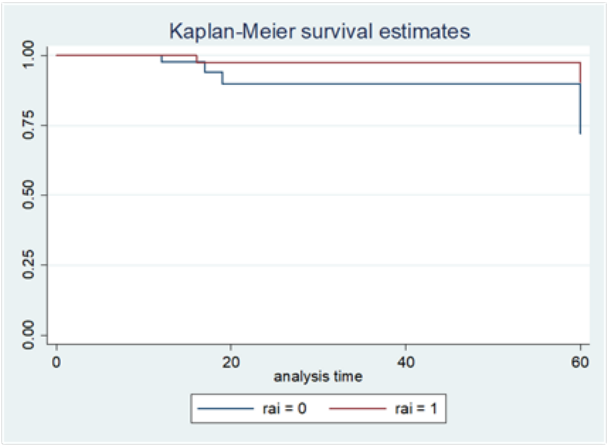

Figure 3. Kaplan-Meier estimates of recurrence rates in low-risk PTMC patients stratified according to RAI (*p*=0.07).

Discussion

The prevalence of PTMC in this study was 29.88% with female predominance (91.11%) similar with findings in other studies.[4,11,19] Our study included patients who had low-risk PTMC or stage I disease, for which RAI remnant ablation is not recommended.[5] The recurrence rate of patients who did not undergo RAI remnant ablation was five times faster than the recurrence rate of patients who underwent RAI remnant ablation but this was not statistically significant. Our data support the findings of previous studies that showed RAI remnant ablation did not decrease disease recurrence in PTMC patients.[15-18]

Although PTMC has an indolent course, it remains the cause of mortality or substantial morbidity in a small subset of patients. Mazzaferri reported locoregional recurrences as high as 5.9% and distant recurrences at 1.5%.[21] The prevalence of recurrence in our study was 6.67% occurring at a median of 18 months. The estimated recurrence rate for the whole cohort was 1.25% at one year and 6.02% at two and five years. The estimated recurrence rates between the two groups were not significantly different (*P*=0.09) even after controlling for the effect of tumor size (*P*=0.07). These findings are similar with PTMC recurrence data reported in literature.

Several studies on RAI remnant ablation and PTMC recurrence also showed conflicting results. Creach et al. showed that disease recurrence among patients with PTMC was significantly correlated with no RAI remnant ablation (*P*<0.0001), histological tumor size >0.8 cm (*P*=0.01), age <45 years (*P*=0.04), and positive lymph nodes. The five-year recurrence-free survival for patients treated with RAI remnant ablation was 95.0% versus 78.6% (*P*<0.0001) for patients not treated with RAI remnant ablation.[10] Other studies have also shown that no RAI remnant ablation was an independent risk factor for disease recurrence among patients with PTMC.[11-13] These studies included all patients who had low, intermediate and high-risk PTMC. Studies specifically involving patients with low and intermediate risk PTMC showed that RAI remnant ablation did not prevent disease recurrence in these patients.[18] In this study by Kim et al., low-risk PTMC was defined as patients with intrathyroidal PTMC who underwent complete tumor resection. PTMC with microscopic extrathyroidal extension, cervical lymph node

Table II. Characteristics Of Low-Risk PTMC Patients With Recurrence

Patient	Age (yr)	Gender	Tumor size (cm)	Tumor variant	Multifocality	Laterality	RAI	Follow up (mo)	Recurtime (mo)	Recur site
1	54	F	1,0.4	CV	M	L	Y	40	16	LN
2	46	M	0.8	SV	U	L	Y	96	62	TB
3	61	F	0.2	FV	U	L	N	51	19	TB
4	57	F	1	FV	U	L	N	114	70	LN
5	68	F	0.2	FV	U	R	N	42	12	TB
6	28	F	0.1	OV	U	L	N	31	17	LN

CV, classical variant; SV, sclerosing variant; FV, follicular variant; OV, oncocytic variant; M, multifocal; U, unifocal; L, left; R, right; LN, lymph nodes; TB, thyroid bed

metastases or multifocality were classified as intermediate-risk PTMC. This study involved 704 patients with low-risk and intermediate-risk PTMC and the likelihood ratio for recurrence did not differ significantly between the no RAI and RAI ablation groups in any of the patients with PTMC (*P*=0.17). Other studies also showed similar findings that RAI remnant ablation does not decrease disease recurrence and thyroid cancer-related mortality among patients with PTMC.[15-17]

Although a trend of decreased disease recurrence with RAI remnant ablation in our study was seen, this was not statistically significant. RAI therapy is also not without risks and has been shown to increase the risk of secondary primary malignancies.[29,30] In our cohort, only two patients had a history of RAI for previous hyperthyroidism and both of them developed disease recurrence. In the analysis of patients in the National Cancer Institute's Surveillance, Epidemiology, and End Results database who had low-risk well-differentiated cancer, the excess absolute risk was 4.6 cases of secondary malignancies per 10,000 person-years.[31] Any intervention with a risk of secondary malignancy, such as RAI for patients with low-risk thyroid cancer, warrants a careful analysis of its risk versus benefit. Although no secondary malignancies were seen in our study, this might be due to low RAI doses given and short follow-up durations.

Accurate post-operative risk stratification is important when deciding which patients will benefit from RAI remnant ablation. Durante et al identified very low risk PTMC patients as those with no family history of thyroid cancer, no history of head and neck irradiation, tumor size ≤1 cm, no extension beyond thyroid capsule, unifocal, not aggressive histologic subtype, and not locally invasive. These patients were most likely to experience complete cures with total or near-total thyroidectomy without need for postoperative RAI remnant ablation and TSH suppression.[16] Conversely, in another study, RAI remnant ablation is strongly considered in PTMC patients with complicating factors such as cervical lymphadenopathy, extrathyroidal invasion, age greater than 45 years, aggressive histological subtype, positive thyroid cancer family history and/or distant metastasis .[32]

All recurrences in our study were locoregional and no distant metastases were noted during follow-up. This is similar with findings from active surveillance trials for PTMC wherein locoregional metastases were seen in 0.5 to 4% during follow-up but no distant metastasis or mortality were noted.[33] This supports the recommendation of the use of neck ultrasound and serum Tg for monitoring PTMC patients especially those who did not undergo RAI remnant ablation.[32] Low-risk PTMC patients should be monitored and followed up for long periods of time due to its indolent nature and since recurrences can occur after several years.

Our study has some limitations. Our findings are based on retrospective analyses and affected by selection bias of patients for RAI remnant ablation. Although both groups were comparable at baseline, tumor size was significantly larger in the RAI group than in the No RAI group. Thus, performing Cox regression analysis and controlling for the effect of tumor size showed a higher recurrence rate in the No RAI group than in the RAI group but this was still not statistically significant. Our study included patients with at least one year of follow-up since previous studies showed that most PTMC recurrences occurred as early as two years.[34] However, other studies reported disease recurrences occurring within five years or more.[10] Since PTMC has an indolent course and very low recurrence rate, larger sample sizes with longer follow-up durations are required to detect significant differences in outcomes in future studies.

Conclusion

This study did not provide sufficient evidence that RAI remnant ablation prevents disease recurrence in Filipino patients with low-risk PTMC. Future randomized, prospective trials involving larger sample sizes and longer follow-up duration are necessary to confirm our findings.

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