Jonel Donn Leo S. Gloria, MD, MOH
Alfredo Quintin Y. Pontejos, Jr., MD
Precious Eunice R. Grullo, MD, MPH

Department of Otorhinolaryngology
University of the Philippines – Philippine General Hospital

Risk Factors for Recurrent Papillary Thyroid Carcinoma

ABSTRACT

Objective: To identify risk factors associated with disease recurrence among Filipinos with papillary thyroid carcinoma (PTC).

Methods:

Design: Retrospective Cohort Study

Setting: Tertiary National University Hospital

Participants: 76 patients diagnosed with papillary thyroid carcinoma, classified as low and low-to-intermediate risk (2015 ATA classification) that underwent total thyroidectomy with or without neck dissection from 2010-2014 and were followed up from 10 months to 5 years. Log rank and Cox regression analyses were used to determine significant risk factors for recurrence.

Results: 29 (38.15%) had recurrence**.** On univariate analysis, age, tumor size, multifocality, extrathyroidal extension, presence of lateral neck nodes and RAI therapy were statistically associated with recurrence. However, on multivariate analysis, no clinicopathologic factor was statistically associated with recurrence.

Conclusion: Age of >45 years, female sex, tumor size of >2 cm, multifocality, presence of microscopic extrathyroidal extension and lymph node metastasis might contribute to the recurrence of papillary thyroid cancer while post-operative radioactive ablation may have some protective effect. However, this study suggests that other factors must be included in the model to better understand the relationship between these factors and recurrence.

Keywords: *papillary thyroid cancer, thyroid neoplasm, recurrence*

Thyroid cancer was the most frequent head and neck cancer in the Philippines in 2012[1] and continues to rank among the most common reasons for admission at the Philippine General Hospital-Department of Otorhinolaryngology (PGH-ORL). A review of all thyroid cases admitted at the PGH-ORL from January 2006 to December 2010 revealed 415 thyroid malignancies managed, of which 82.9% were papillary thyroid carcinoma (PTC).[2]

Correspondence: Dr. Alfredo Quintin Y. Pontejos, Jr.
Department of Otorhinolaryngology
Ward 10, Philippine General Hospital
University of the Philippines, Manila
Taft Avenue, Ermita, Manila 1000
Philippines
Phone: (632) 554 8400 local 2152
Email: docpontejosjr@yahoo.com

The authors declare that this represents original material, that the manuscript has been read and approved by all the authors, that the requirements for authorship have been met by each author, and that each author believes that the manuscript represents honest work.

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The primary treatment of PTC is still surgery (thyroidectomy) and when appropriate, a neck dissection.[3,4,5] In our setting, a considerable subset of PTC tends to become more aggressive and recurs even with adequate surgical and medical management. While local and regional recurrences of PTC after surgery have ranged from 5-10%,[6] a 2010 study among Filipinos with thyroid cancer claimed recurrence rates as high as 25%.[7] Recurrences may be local (primary site and adjacent structures), regional (cervical lymph nodes) or distant and impact negatively on patients' quality of life with increased morbidity.

The extent of surgery and need for adjuvant treatment depend on several prognostic factors that influence risk stratification of patients in terms of recurrence and survival. Several studies have identified clinicopathologic factors predictive of increased risk of recurrence among patients with PTC, including age, sex, tumor size, cervical lymph node metastasis, extrathyroidal invasion, bilaterality/multifocality and post-operative RAI therapy.[8-17]

In order to determine specific patient- and disease-related factors associated with PTC recurrence among our patient population that are essential for developing initial treatment and follow-up schemes and establishing the need for adjuvant treatment in our setting, this study aims to determine factors that are associated with recurrence of PTC among patients admitted at PGH-ORL in terms of age during initial surgery, sex, tumor size, multifocality, extrathyroidal extension, lymph node metastasis and post-operative RAI therapy.

METHODS

With institutional review board approval, this retrospective cohort study reviewed the records of 86 patients diagnosed with papillary thyroid carcinoma that underwent total thyroidectomy with or without neck dissection at the PGH-ORL from January 2010 to December 2014 and followed up for at least 10 months. Papillary thyroid carcinoma recurrence was defined as the reappearance of PTC after a period of at least 10 months from initial surgery including both local and regional recurrences.[7]

Medical records (including operative records and histopathology results) were reviewed for the following data: age (years) at the time of initial surgery, sex, tumor size, multifocality, extrathyroidal extension, lymph node metastasis, post-operative RAI therapy and length of follow-up. Considered for inclusion were records of patients with Papillary Thyroid Cancer on histopathologic result and low and low-to-intermediate risk 2015 ATA classification. Excluded were records of cases with no definite histopathologic result and high-risk 2015 American Thyroid Association (ATA) classification (residual disease, gross extrathyroidal extension, distant metastasis) as these patients had high risk of recurrence.[18]

Data was tabulated using Microsoft Excel version 2013 (Microsoft, Chicago, USA) and means and proportions were obtained. Univariate analysis was performed using log-rank test. The outcome of interest was recurrence, established by imaging (ultrasonography or computed tomography), thyroglobulin levels, thyroid scintigraphy, or histopathology. Variables with $p < .25$ on univariate analysis were included in the multivariate analysis using Cox regression. Kaplan-Meier curves were obtained. Data were analyzed using STATA version 13.1 (StataCorp, TX, USA).

RESULTS

Records of 76 patients (21 males, 55 females) were included in this series. The mean age of the patients was 44 ± 2 years (range 15-77 years). The average tumor size was 3.96 ± 0.29 cm (range 0.3 to 14.5 cm). 29 (38.15%) had recurrences while 47 had no observed recurrence on the cut-off date. The sites of recurrences follows: 3, thyroid bed only; 17, lateral neck (16 unilateral and 1 bilateral); 9, both thyroid bed and lateral neck (6 in the thyroid bed and unilateral neck and 3 in the thyroid bed and bilateral neck). The 10 excluded records were those of 2 patients that had no definite histopathologic result and 8 cases with high risk 2015 ATA classification. *Table 1* summarizes the clinicopathologic profiles of the patients included in the series.

With cut-off $p < .25$, age ($p = .01$), tumor size ($p = .2$), multifocality ($p = .04$), extrathyroidal extension ($p = .02$), presence of lateral neck nodes ($p = .03$) and RAI therapy ($p = .2$) were included in multivariate analysis on which no clinicopathologic factor was statistically associated with recurrence. This indicates that other factors affecting recurrence are missing in the model (R^2=0.3776). *Table 2* summarizes the results (p values, hazards ratios and confidence intervals) of both univariate and multivariate logistic regression analyses on the factors studied.

In this study, those with age > 45 years old had 1.93 times higher risk of having a recurrence than those </= 45 years old . Tumor size of >2 to 4 cm and >4 cm had 59% and 74% increased risk of recurrence compared to tumors <2 cm in size, respectively. The presence of multifocality increased the risk of recurrence by 69%. The risk of recurrence was 1.31 times higher if extrathyroidal extension was present. Unilateral neck nodes and bilateral neck nodes increased the risk of recurrence 2.06 times and 1.47 times, respectively. RAI therapy decreased the risk of recurrence by 51%. *Figure 1* shows the Kaplan-Meier curve analysis for each clinicopathologic factor studied. The estimated 5-year recurrence-free estimate is 32.87%.

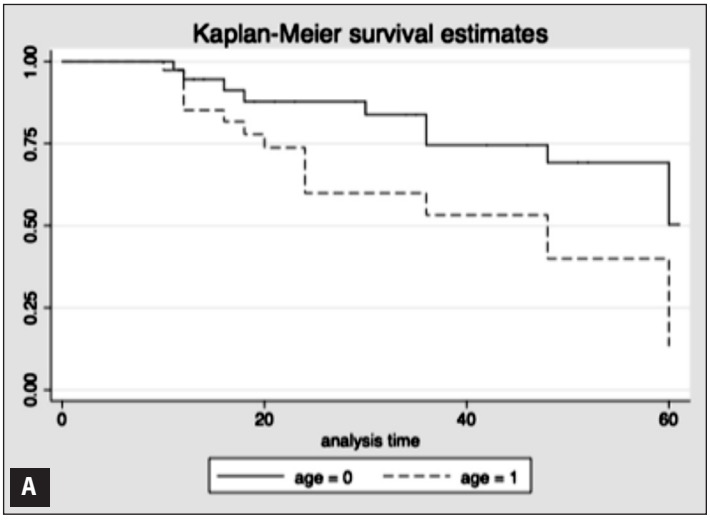
Table 1. Clinicopathologic profile of the patients

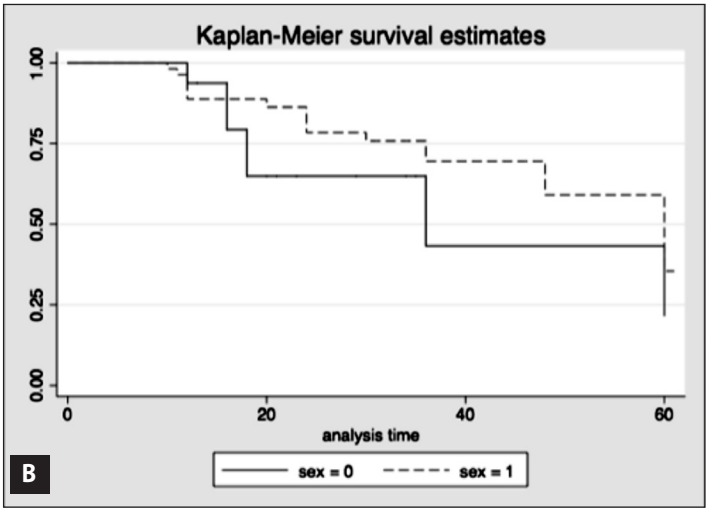
Clinicopathologic factors		Without recurrence n = 47	With recurrence n = 29
Age (years)	≤ 45	28 (60%)	11 (38%)
	> 45	19 (40%)	18 (62%)
Sex	male	14 (30%)	7 (24%)
	female	33 (70%)	22 (76%)
Tumor Size (cm)	≤ 2	17 (36%)	7 (24%)
	> 2 to 4	16 (34%)	6 (21%)
	> 4	14 (30%)	16 (55%)
Multifocality	absent	32 (68%)	12 (41%)
	present	15 (32%)	17 (59%)
Extrathyroidal extension	absent	38 (81%)	11 (38%)
	present	9 (19%)	18 (62%)
Central neck nodes	absent	33 (70%)	21 (72%)
	present	14 (30%)	8 (28%)
Lateral neck nodes	absent	32 (68%)	14 (48%)
	unilateral	14 (30%)	12 (41%)
	bilateral	1 (2%)	3 (11%)
RAI therapy	absent	20 (43%)	19 (66%)
	present	27 (57%)	10 (34%)
Follow-up time (months)		30 (sd:3)	32 (sd:4)

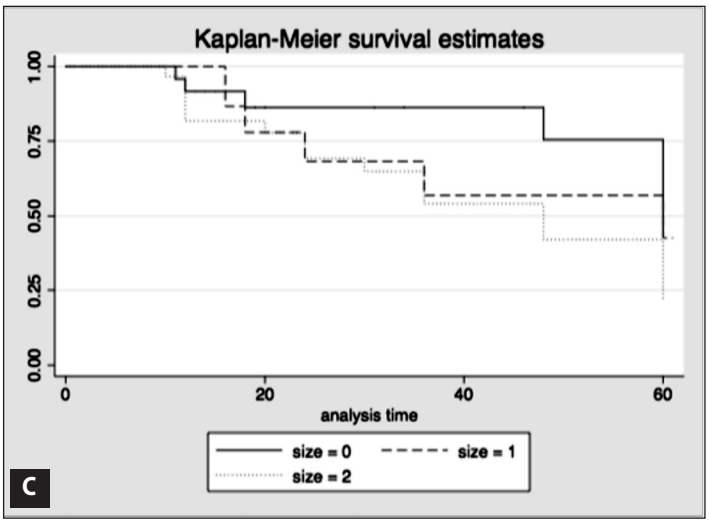
Table 2. Univariate and multivariate analyses of the factors associated with PTC recurrence

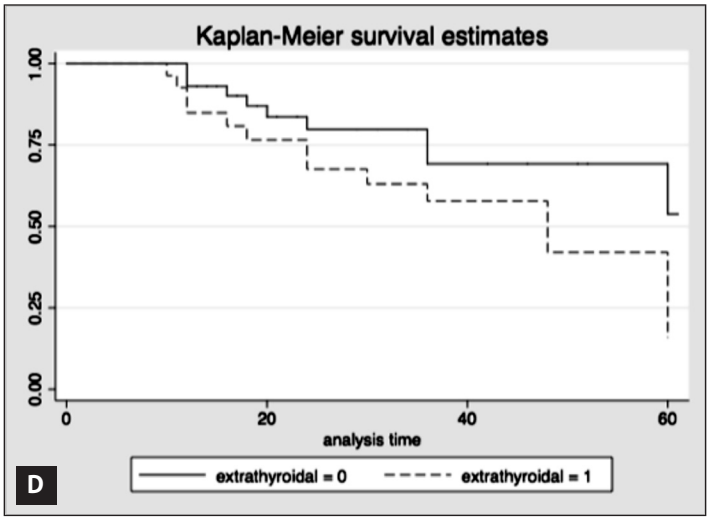
Clinicopathologic Factors		Univariate Analysis	Multivariate Analysis		
		p	HR	CI	p
Age	≤ 45	.01	1.93	0.78-4.80	.10
Sex	female	.27			
Tumor Size	> 2 to 4	.20	1.59	0.49-5.24	.44
	> 4		1.74	0.68-4.48	.25
Multifocality	present	.04	1.69	0.71-4.04	.25
Extrathyroidal extension	present	.02	1.31	0.56-3.1	.53
Central neck nodes	present	.74			
Lateral neck nodes	unilateral	.03	2.06	0.83-5.1	.12
	bilateral		1.47	0.33-6.47	.61
RAI therapy	present	.20	0.49	0.21-1.15	.10

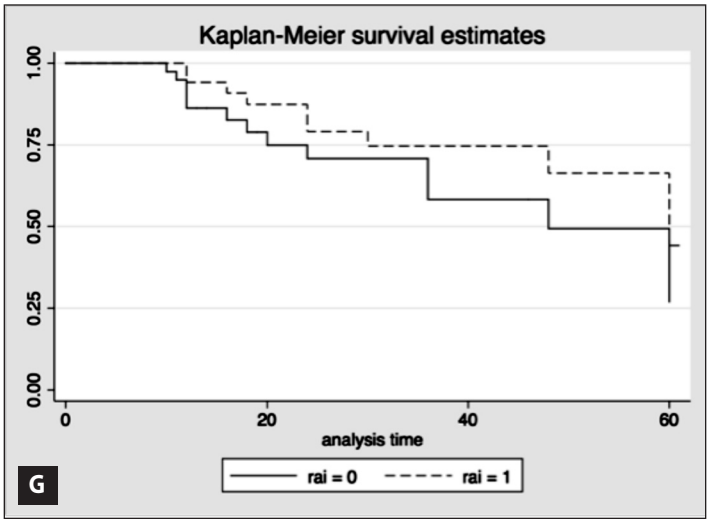
Note: Blacked out cells are not included in the multivariate analysis; cut-off p<0.25

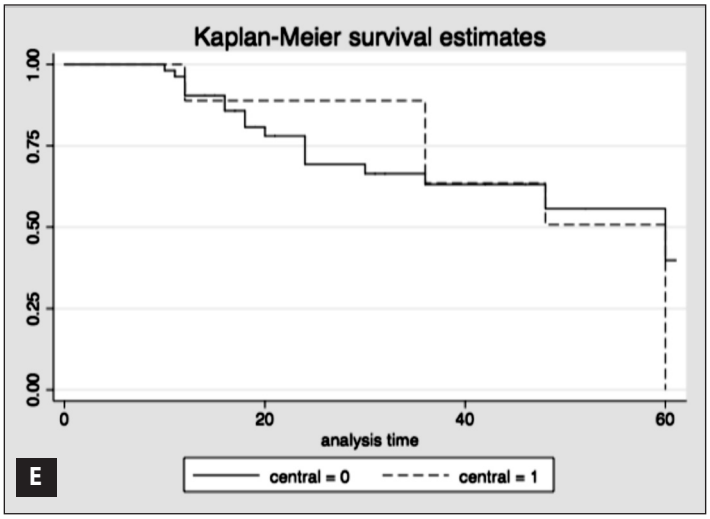












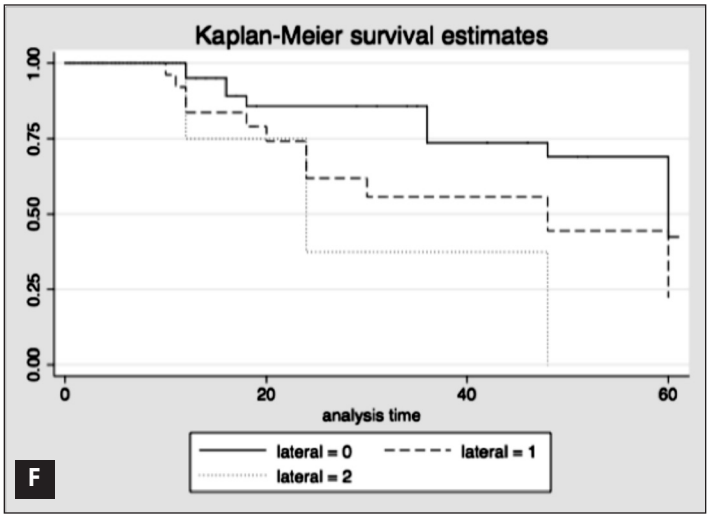


Figure 1. Kaplan-Meier disease-free estimate curves of clinicopathologic factors for papillary thyroid cancer recurrence. **A.** Age. Note that age >45 (dash) has a lower recurrence-free estimate than younger patients **B.** Sex. Males (solid line) have a lower recurrence free estimate than females but not statistically significant. **C.** Tumor size. Tumor size of 2-4 cm (dash) and more than 4 cm (dotted line) have a lower recurrence free estimate than size less than 2 cm (solid). **D.** Extrathyroidal extension. Recurrence free estimate is lower when microscopic extrathyroidal extension is present (dash). **E.** Presence of central neck node. The presence of central neck node metastasis (dash) has a higher recurrence-free estimate compared to its absence but only during the early periods of observation. **F.** Presence of lateral neck node. Those without lateral neck node (solid) have a significantly higher recurrence free estimate compared to unilateral (dash) and bilateral (dotted) neck node metastasis. **G.** Postsurgical radio¬active iodine (RAI) ablation. The use of post-op RAI (dash) has higher recurrence-free estimate compared to cases without post-op RAI although not statistically significant.

DISCUSSION

This study suggests that age of >45 years, female sex, tumor size of >2 cm, multifocality, presence of extrathyroidal extension and lymph node metastasis may increase the risk of papillary thyroid recurrence although the associations did not reach statistical significance. Post-operative RAI ablation may decrease the risk of recurrence although this also did not reach statistical significance. *(Table 2)* These factors are similar to reports in other populations.[11,16]

The 45-year-old age cut-off by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology was also shown to be a risk factor for papillary thyroid cancer recurrence among Filipinos in this study.[4] In this study, PTC patients with multifocal disease had higher risk of developing recurrence than those with unifocal disease. This echoes the findings of Qu *et al.*[19] that increasing number of tumor foci of PTC are associated with a tendency toward more aggressive features, shorter recurrence-free survival and may be a possible indicator of cancer death. The number of tumor foci might also represent the tumor burden in PTC patients,[19] consistent with another study by Lin *et al.* where 52.9% of recurrent multicentric PTC patients were diagnosed within the first year of thyroidectomy.[20] This study showed that extrathyroidal extension carries an increased risk of developing recurrence. In comparison, Arora *et al.* found a 6.4-fold increased risk

of recurrence and significantly decreased disease-free survival in PTC patients with macroscopic extrathyroidal extension[21] and nodal metastasis has been reported to increase the risk of recurrence.[19, 21]

The use of post-operative RAI therapy based on our results is protective with an HR of 0.49. Unlike in high risk patients where the evidence for the benefits of RAI are strong, the ATA 2015 guideline reported that there are conflicting observational data in the use of post-op RAI among low and low-to intermediate risk patients.[18] According to the UP-PGH Revised Clinical Practice Guidelines for the Management of Well-Differentiated Thyroid Carcinoma of Follicular Cell Origin in 2012, the use of adjuvant RAI treatment in well-differentiated thyroid cancer has been shown to significantly decrease disease recurrence and cause-specific mortality.[5] Our study supports this recommendation.

There are several limitations of this study. First is the potential for selection bias in a retrospective study. In this study, it was assumed that all tumors were resected if no residual tumor was indicated in the operative technique or no positive margins were noted on histopathologic result. Initial thyroglobulin levels were not available for all patients. Second, the timing of recurrence is relative. For some patients, recurrence was detected due to regular determination of thyroglobulin. For some, imaging was done after a neck mass was noted. In effect, the diagnosis of recurrence might be later than it really is. This could decrease the possible relationship of recurrence to the variables studied. Third, the variables measured in this study were limited to age (years) at the time of initial surgery, sex, tumor size, multifocality, microscopic extrathyroidal extension, lymph node metastasis and post-operative RAI therapy. Other variables that could affect recurrence like molecular mutation status and timeliness of RAI therapy were not measured.

In conclusion, age of >45 years, female sex, tumor size of >2 cm, multifocality, presence of microscopic extrathyroidal extension and lymph node metastasis might contribute to the recurrence of papillary thyroid cancer while post-operative radioactive ablation may have some protective effect. However, the findings in this study suggest that other factors must be included in the model in order to better understand the relationship between these factors and recurrence.

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