

Risk Factors for Locoregional Metastasis, Distant Metastasis and Persistent Disease in Micropapillary Thyroid Cancer Among Filipinos

Armand Rosaurus A. Labitag, M.D.*; Eduardo Thomas Aquino, M.D.*; Marjorie Ramos, M.D.*; Kevin Carl Santos**

Abstract

Background: Micropapillary Thyroid Cancer (MPTC) is defined as papillary thyroid cancer measuring less than one centimeter in size. Although there have been many studies involving MPTC, there is still a gap in the understanding of the behavior of MPTC in the Filipino population.

Objectives: This study aims to determine risk factors and prevalence of locoregional and distant metastasis upon diagnosis and the risk factors for persistent disease after thyroidectomy among patients with MPTC.

Methods: : This is a retrospective study that included all patients with histopathology result of MPTC from January 1, 2004 to December 31, 2012. Patients who had accompanying well differentiated thyroid tumors other than MPTC and those patients with a diagnosis of MPTC with no follow up after the surgery were excluded.

Results: A total of 109 patients were eligible for the study. The mean age was 46.06 years with majority being female (96.3%). The average tumor size was 0.502 cm. Seventy-five

(68.81%) received Radioactive Iodine Therapy (RAI) after thyroidectomy. Nineteen patients (17.92%) had multifocal disease while 11 (10.09%) had multicentric disease. Fifteen patients (13.76%) had locoregional metastasis while eight (7.34%) had distant metastasis on diagnosis. Out of the 91 patients included for analysis of persistent disease, eight patients (8.79%) had persistent disease. Exact logistic regression showed that locoregional metastasis ($p=0.0044$) is a risk factor for distant metastasis at diagnosis. Age, sex, tumor size, multifocality, multicentricity, RAI, and extent of surgery did not reach statistical significance as independent risk factor for locoregional, distant metastasis on diagnosis, and persistent disease.

Conclusion: Although MPTC is considered an indolent type of well differentiated thyroid cancer, there are certain patients who may present with metastasis at diagnosis. Our data showed that locoregional metastasis is a risk factor for distant metastasis on diagnosis in patients having MPTC.

Keywords: Risk Factors, Metastasis, Micropapillary Thyroid Cancer

Introduction

Micropapillary Thyroid Cancer (MPTC) is defined as papillary thyroid cancer measuring less than one centimeter in size.¹ The clinical behavior of this tumor tends to be slow with an excellent prognosis. Most of the series have reported a very low mortality rate between 0% and 0.4%.^{2,3,4} Certain characteristics of MPTC such as multifocality, bilaterality, and minor extrathyroidal extension are found to have a comparable frequency with papillary thyroid cancer. Lymph node metastases and distal metastases, however, occur with lower frequency.^{3,4,5}

Until now, there has been no consensus on the optimal management of MPTC patients. It can range from observation without surgery based on a recent clinical trial

carried out by Japanese authors⁶ to total thyroidectomy with neck dissection followed by radioiodine treatment depending on the presence of aggressive characteristics.⁷ There have also been proposals on stratifying patients with MPTC into high or low risk of recurrence based on some clinical and histological characteristics of patients such as age, sex, tumor size, histological features, multifocality, lymph node involvement, or distant metastases.⁸

Although there have been many studies involving MPTC, there is still a gap in the understanding of the behavior of MPTC in the Filipino population. It has been known that well-differentiated thyroid cancer among Filipinos behave differently when compared to other nationalities. Filipinos are more at risk to develop thyroid malignancy⁹ and have tumors with higher risk of recurrence.¹⁰ Based on these findings, an understanding of the risk factors for aggressiveness of MPTC, such as locoregional and distant metastasis at diagnosis, and factors that could affect persistent disease can benefit in making decisions in the treatment of this supposedly indolent type of thyroid cancer.

Based on previous studies^{5,8} done on MPTC, we hypothesized that age >45 years, multifocality and multicentricity of lesions, female gender, and tumor size

*Section of Endocrinology, Diabetes, and Metabolism, Department of Internal Medicine, St. Luke's Medical Center, Quezon City, Philippines

**School of Statistics, University of the Philippines, Diliman, Quezon City, Philippines

Corresponding Author: Armand Rosaurus A. Labitag, M.D.,
St. Lukes Medical Center, Quezon City, Philippines
Email: armandlabitag@gmail.com

>0.5 cm increase the risk for locoregional metastasis on diagnosis. Aside from presence of locoregional metastasis, the previously mentioned risk factors were also inferred to increase the risk for distant metastasis on diagnosis. For persistent disease, we hypothesized that age >45 years, multifocality and multicentricity of lesions, female gender, and tumor size >0.5 cm, conservative thyroid surgery (thyroid lobectomy as opposed to total or subtotal thyroidectomy), and absence of Radioactive Iodine Therapy (RAI) post-thyroidectomy favor increased risk.

Objectives

1. To determine the risk factors and prevalence of having locoregional metastasis and distant metastasis at diagnosis.
2. To determine the factors that can increase the persistence of MPTC.

Methodology

Study Design

This is a retrospective study that included all patients who had thyroidectomy in St. Luke's Medical Center, Quezon City and had a histopathology result of MPTC from January 1, 2004 to December 31, 2012. The database from the Pathology Department was reviewed to see who had a final histopathology of MPTC after thyroidectomy. The study variables were patient age, gender, tumor size, multifocality, multicentricity, presence of locoregional and distant metastasis at diagnosis, as well as the extent of surgery and whether RAI was administered. In order to determine the frequency of persistent disease, chart review was done to check laboratory results during follow up of patients.

Inclusion/Exclusion Criteria:

The inclusion criteria included patients greater than 18 years old who had thyroidectomy and had a histopathology result of MPTC. Those patients who had accompanying well differentiated thyroid tumors other than MPTC and those patients with a diagnosis of MPTC with no follow up after the surgery were excluded from the study.

Definition of Terms

Persistent disease is defined as the development of any of the following three findings: positive Iodine-131 (I-131) Whole Body Scan (WBS) on clinical report, positive pathology if repeat FNAB was done on new nodules, or development of a mass on thyroid bed or lymphadenopathy after thyroidectomy with positive pathology if FNAB was done.

Locoregional metastasis is defined as metastasis to the cervical lymph nodes, pretracheal, prelaryngeal lymph

nodes, up to superior mediastinal lymph nodes.

Distant metastasis pertains to metastasis beyond the superior mediastinum.

Data Analysis

A computed sample size of 350 was required. Logistic regression analysis was performed to determine the correlation between various parameters and the development of persistent disease as well as for determining the risk factors of locoregional and distant metastasis at diagnosis. Continuous variables were expressed as means $\pm$ standard deviation and categorical variables as percentages.

Results

One hundred seventy eight patients with MPTC were identified in the histopathology database of St Luke's Medical Center, Quezon City from January 1, 2004 to December 31, 2012. Out of these, only 109 patients had follow-up and qualified for inclusion for data analysis. Their characteristics are shown in Table I.

Table I. Characteristics of Included Patients with Micropapillary Thyroid Cancer

N		109
Mean Age in years		46.06 (SD 11.35)
Sex	Female	105 (96.3%)
	Male	4 (3.7%)
Average Tumor Size		0.5022 cm (SD 0.25)
Multifocal		19 (17.92%)
Multicentric		11 (10.09%)
Extent of Thyroidectomy	Total	85 (77.98%)
	Subtotal	15 (13.76%)
	Lobectomy	9 (8.26%)
Locoregional Metastasis		15 (13.76%)
Distant Metastasis		8 (7.34%)
Post Thyroidectomy RAI		75 (68.81%)
Mean Follow Up in years		4.67 (SD 2.38)

The age of the patients included in the study ranged from 23 to 79 years with the mean of 46 years. Majority were females (96.3%). The size of the tumor ranged from 0.1 to 0.9 cm. Ninety-three (85.32%) patients were Stage I, four (3.67%) patients were stage II, three (2.75%) patients were stage III, five (4.58%) patients were stage IVA, while four (3.66%) patients were stage IVC using the 2010 version of the TNM Classification System for Differentiated Thyroid Carcinoma staging of the AJCC. The mean dose that was given in patients who received RAI after thyroidectomy was 99.38 mci (range 50 to 150 mci) (Table II).

Table II. Characteristics of patients with locoregional metastasis on diagnosis

Age	Sex	Size (cm)	Multifocal or Multicentric	Extent of Thyroidectomy	Level of Cervical Lymph Node Seen with Metastasis at Diagnosis	TNM Stage
66	F	0.3	No	Total Thyroidectomy	Level VI	Stage III (T1N1aM0)
35	F	0.8	No	Total Thyroidectomy	Level V	Stage I (T1N1bM0)
61	F	0.7, 0.4	Multifocal	Total Thyroidectomy	Level VI	Stage III (T1N1aM0)
31	F	0.2	No	Total Thyroidectomy	Level II	Stage I (T1N1bM0)
51	F	0.2	No	Total Thyroidectomy	Level V	Stage IVA (T1N1bM0)
51	F	0.1, 0.4, 0.7	Multifocal	Total Thyroidectomy	Level V	Stage IVA (T1N1bM0)
59	F	0.5	No	Total Thyroidectomy	Level V	Stage IVA (T1N1bM0)
45	F	0.2	No	Total Thyroidectomy	Level I	Stage IVA (T1N1bM0)
59	F	0.3, 0.4	Multifocal	Total Thyroidectomy	Level VI	Stage III (T1N1aM0)
44	F	0.3	No	Total Thyroidectomy	Level V	Stage I (T1N1bM0)
63	F	0.4	No	Total Thyroidectomy	Level V	Stage IVA (T1N1bM0)
31	F	0.3, 0.4	Multifocal	Total Thyroidectomy	Level VI	Stage I (T1N1aM0)
25	F	0.9	No	Total Thyroidectomy	Level III and IV	Stage I (T1N1bM0)
38	F	0.8	No	Total Thyroidectomy	Level III	Stage I (T1N1bM0)
41	F	0.4	No	Total Thyroidectomy	Level VI	Stage I (T1N1aM0)

Table III. Exact logistic regression analysis for correlation of risk factors for locoregional metastasis on diagnosis

Independent Variables	Coefficient Estimates	Odds Ratio	95% CI for OR		p-value
Age	0.006567	1.007	0.958	1.057	0.7957
Sex	-0.1765	0.838	0	5.361	0.8897
Tumor Size	-0.4797	0.619	0.049	6.895	0.7338
Multicentric	-1.2508	0.286	0	1.578	0.2488
Multifocal	1.0388	2.826	0.519	13.591	0.2615

Locoregional metastasis upon diagnosis was identified through positive lymph nodes by histopathology or I-131 WBS after thyroidectomy. All of the patients who had locoregional metastasis were females with a mean age of 46.66 years. Most of the locoregional metastasis was seen in the Level V of the cervical group of lymph nodes. The mean tumor size was 0.46 cm. In the analysis of exact logistic regression, none of the independent variables reached statistical significance (Table III).

Distant metastasis was detected with I-131 WBS done after the first dose of RAI was given. As seen in Table IV, the mean age of these patients was 44.5 years with a mean tumor size of 0.51 cm. One patient had multiple distant metastases in three separate sites on diagnosis (left lung, right ilium, and right femur) while the rest had single distant metastasis. Out of the eight patients with distant metastasis, five (62.5%) had an accompanying locoregional metastasis on diagnosis. The presence of locoregional metastasis showed positive correlation with the presence of distant metastasis at diagnosis (Table V).

In the analysis for persistent disease, only those without distant and locoregional metastasis at diagnosis, which add up to 91 patients, were included. The prevalence of persistent disease in our study is 8.79%. As seen in Table VI, majority of persistent disease were seen in the region of the neck. The average year of detection of persistent disease was 3.125 years after thyroidectomy. They were detected after a repeat I-131 WBS on surveillance. Out of the seven independent variables tested for correlation with persistent disease, none reached statistical significance (Table VII).

Discussion

Our study showed that locoregional metastasis is an independent risk factor for distant metastasis in MPTC. None of the hypothesized risk factors proved to be statistically

Table IV. Characteristics of Patients with Distant Metastasis on Diagnosis

Age	Sex	Level of Cervical Lymph Node Seen with Metastasis at Diagnosis	Size (cm)	Multifocal or Multicentric	Extent of Surgery	Area of Distant Metastasis	TNM Stage
51	F	Level V	0.2	No	Total Thyroidectomy	Inferior Mediastinum	Stage IVC (T1N1bM1)
44	F	Level V	0.3	No	Total Thyroidectomy	Anterior Mediastinum	Stage II (T1N1bM1)
63	F	Level V	0.4	No	Total Thyroidectomy	Inferior Mediastinum	Stage IVC (T1N1bM1)
53	F	None	0.6	No	Total Thyroidectomy	Left Lung	Stage IVC (T1N0M1)
37	F	None	0.5	No	Total Thyroidectomy	Frontal Bone	Stage II (T1N0M1)
31	F	Level VI	0.3 and 0.4	Multifocal	Total Thyroidectomy	Left Lung, Right Ilium, and Right Femur	Stage II (T1N1aM1)
52	F	None	0.8	No	Total Thyroidectomy	Acetabulum	Stage IVC (T1N0M1)
25	F	Level III and IV	0.9	No	Total Thyroidectomy	Sternum	Stage II (T1N1bM1)

Table V. Exact Logistic Regression Analysis for Correlation of Risk Factors for Distant Metastasis on Diagnosis

Independent Variables	Coefficient Estimates	Odds Ratio	95% CI for OR		p-value
Age	-0.0104	0.99	0.925	1.057	0.7713
Sex	1.7836	5.951	0	41.18	1
Tumor Size	0.8022	2.23	0.08	63.966	0.6692
Locoregional Metastasis	2.471	11.835	2.022	82.754	0.0044
Multicentric	0.8181	2.266	0	17.236	1
Multifocal	-0.8037	0.448	0.008	5.114	0.8844

Table VI. Characteristics of patients with Persistent Disease

Age	Sex	Size of tumor (cm)	Multifocal/Multicentric	Extent of Thyroidectomy	RAI dose	Area of Persistent Disease	Time of Detection
49	F	0.7, 0.4	Multifocal	Total Thyroidectomy	100 mci	Anterior Neck	1 year
58	F	0.6, 0.5	Multicentric	Total Thyroidectomy	100 mci	Submandibular Area	3 years
45	F	0.8	No	Total Thyroidectomy	100 mci	Mandible	2 years
33	F	0.3, 0.3, 0.1	Multifocal and Multicentric	Total Thyroidectomy	150 mci	Supraclavicular Lymph Node	4 years
36	F	0.4	No	Left Thyroidectomy	None	Anterior Thorax	4 years
61	M	0.5	No	Total Thyroidectomy	None	Submandibular area	3 years
52	F	0.2, 0.3, 0.9 cm	Multifocal	Total Thyroidectomy	None	Jugular Region	3 years
60	F	0.1	No	Total Thyroidectomy	None	Submandibular Area	3 years

Table VII. Multiple Logistic Regression Analysis for Correlation of Risk Factors for Persistent Disease

Independent Variables	Coefficient Estimates	Odds Ratio	95% CI for OR		p-value
RAI	-0.9568	0.384	0.055	2.623	0.4116
Age	0.0295	1.03	0.96	1.106	0.4148
Sex	0.7643	2.147	0.032	35.916	0.9898
Tumor Size	-0.506	0.603	0.022	16.927	0.8051
Locoregional Metastasis	0.7322	2.08	0.152	19.685	0.7578
Multicentric	1.1099	3.034	0.346	26.468	0.4001
Multifocal	-0.4502	0.637	0.076	2.922	0.806

significant for increased risk of locoregional metastasis on diagnosis and persistent disease. Furthermore, the prevalence of locoregional metastasis on diagnosis in our study was 13.76%. This coincides with the research done by Roti et al. with a 13% prevalence of local node metastasis on diagnosis.⁸ On the other hand, the prevalence of distant metastasis at diagnosis of 7.34% was significantly higher compared with findings in other studies involving Filipinos. Silva et al.¹³ found one patient with bone metastasis out of 22 patients with MPTC while Guerrero et al. reported only two cases with brain metastasis on diagnosis.¹² The possible explanation to the discrepancy in this finding is the use of I-131 WBS after thyroidectomy in our patients.

Although it has been seen in some studies that Filipinos have a higher risk to develop thyroid malignancy⁹ and recurrence¹⁰ compared to our Caucasian counterpart, there have been no clear risk factors associated to this finding. Without the aid of genetic studies, it is difficult to conclude that Filipino ethnicity plays a role in the increased prevalence and aggressiveness of well-differentiated thyroid malignancy.

MPTC had been diagnosed with increased frequency mainly due to the widespread use of ultrasound-guided FNAB and thyroid surgery. The prevalence of MPTC is around 10 to 40% in some series.^{5, 6, 11} This coincides with a recent research done by Guerrero et al. among Filipinos which showed that MPTC had a prevalence of 22%.¹² In a review of 5035 cases in a metaanalysis done by Roti et al.⁵, it was seen that 71% were incidentally discovered after surgery for other thyroid disorders. Results of several studies reveal predominance in females with a ratio of 4.8 female for every one male with most tumors having a median size ranging from 4.0 mm to 8.0 mm.⁵ Multifocal tumors can be seen in up to 57% while multicentric tumors range from three to 48% of cases.⁵

Risk factors for lymph node metastasis on diagnosis have been identified in several studies. A metaanalysis done by Roti et al. showed that larger tumor size, follicular variant, and extracapsular extension was associated with a higher prevalence of lymph node metastasis at diagnosis.⁵ However, there are some studies that dispute tumor size as a risk factor for lymph node metastasis. Chow et al.⁴ and Pelizzo et al.¹¹ did not find a difference in the prevalence of lymph node metastasis in tumors greater than or less than 5.0 mm in size. Tumor size (OR 0.619) was not also seen as a risk factor for locoregional metastasis on diagnosis in our study. Although there was a trend for multifocality (OR=2.82) as a possible risk factor for locoregional metastasis upon diagnosis, it did not have statistical power (p-value= 0.2615).

Several risk factors for distant metastasis are discussed in different studies. According to Roti, distant metastasis correlated positively with the diameter of tumor, advancing age, lymph node metastasis at diagnosis and follicular variant of MPTC.⁸ Among the individual risk factors included in our study, locoregional metastasis on diagnosis was found to significantly increase distant metastasis on diagnosis with an Odds Ratio of 11.835 (p-value = 0.0044).

Recurrent disease is a very important aspect of cancer treatment since it is associated with poor quality of life for cancer patients and their families.¹⁴ Lymph node recurrent disease is seen in 2.4% of MPTC patients while recurrent disease in distant areas is seen in 0.27% of cases.^{5, 15} Certain risk factors for recurrent disease include young age, multifocality, and lymph node involvement at diagnosis are significant for recurrent disease based on Roti et al.⁵ A study done by Mantinan et al.¹⁶ also agrees that multifocality is an independent predictor of relapse while Creach et al.¹⁷ associated lymph node status and tumor size for recurrence in their cohort. Since the average follow up of our patients is only 4.67 years, we can only assess for persistence of disease, which in our study amounts to a prevalence of 8.79%. There was a trend for male gender, multifocality, and multicentricity for persistent disease in our population. However, these factors did not reach statistical significance.

There is still no consensus for the management of MPTC.¹⁶ Extent of surgery for MPTC varies among the different scientific societies. The American Thyroid Association (ATA) recommends thyroid lobectomy for patients with small, low risk, isolated intrathyroidal papillary carcinoma.² The European Thyroid Association recommends partial thyroidectomy¹⁸ while the British Thyroid Association recommends lobectomy.¹⁹ The European Society of Medical Oncology also recommends less extensive surgical procedures for unifocal differentiated thyroid cancer diagnosed at final histopathology after surgery for benign thyroid disease as long as the tumor is intrathyroidal, small, and of favorable histologic type.²⁰ Multiple logistic regression analysis showed a lower risk of persistent disease (OR 0.637) with total thyroidectomy compared to lobectomy in our patients; however, this also did not reach statistical significance. This was similar to the findings in the metaanalysis of Roti et al. where more extensive surgery favors lower recurrence in MPTC.⁵

Based on the recommendations of ATA, RAI is not recommended for patients with unifocal cancer <1 cm without other higher risk features.² However, a study by Creach et al. showed that I-131 treatment had a positive correlation with lower recurrence rate among patients with MPTC.¹⁷ Another reason for doing remnant ablation with I-131 is that it increases sensitivity of thyroglobulin for detection of persistent or recurrent disease.²¹ I-131 WBS after high dose RAI also provides additional prognostic information by being able to identify lymph node and distant metastasis more frequently compared to pretreatment I-131 WBS.^{2, 21} Those with distant metastasis seen in our patients benefited from post therapy I-131 WBS since their distant metastasis were detected through this method. In our data, remnant ablation after total thyroidectomy showed a trend for lower risk of persistent disease with an odds ratio of 0.384. However, this did not reach statistical significance.

Conclusion

Although MPTC is considered an indolent type of well differentiated thyroid cancer, there are certain patients who may present with metastasis at diagnosis. At present, it is difficult to distinguish patients with aggressive MPTC from indolent ones. The best practice is to monitor patients with regular clinical examinations and be aggressive in managing patients suspected to have high risk tumors.

Our study was limited by our small sample size. We therefore recommend that a larger population be included in future studies and if possible, a prospective study design be used to further establish risk factors associated with aggressive MPTC.

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