# Association of Lymphovascular Invasion with Metastasis (Locoregional Lymph Node or Distant) among Adult Filipino Patients with Papillary Thyroid Carcinoma: A Case Control Study

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## ABSTRACT

**Background/Objective:** *Papillary thyroid carcinoma is the most common type of thyroid cancer. Treatment includes surgery and remnant ablation with radioactive iodine therapy while follow-up monitoring includes I-131 whole body scans and thyroglobulin monitoring. Lymphovascular invasion (LVI) has been used as a predictor of metastasis in different cancers. Therefore, it might be useful in predicting metastasis in patients with papillary thyroid carcinoma since metastasis in this type of carcinoma travels via the lymphatic route. The purpose of this study was to determine the association of LVI with metastasis among patients with papillary thyroid carcinoma.* **Methodology:** *Records of patients with papillary thyroid carcinoma (histopathologic reports, thyroglobulin levels and I-131 whole body scans) were reviewed. Univariate and multivariate analyses were performed.* **Results:** *A total of 108 subjects were recruited for this study, 47 (43.5%) of which had LVI. There was no association found between LVI and metastasis on baseline ($p = 0.72$) and follow-up scans ($p = 0.07$). However, there was an association between metastasis resolution on follow-up scans and high-dose radioactive treatment ($p = 0.02$) regardless of presence or absence of LVI.* **Conclusion:** *There was a significant association of the presence of LVI with elevated thyroglobulin levels (p-value < 0.0001). A significant association was also seen with LVI and dose activity with resolution of thyroid remnant, locoregional lymph node and distant metastasis($p = 0.02$). Even though no association was seen between LVI and metastasis, a robust percentage of patients with LVI were positive for metastasis on whole body scans.*

Keywords: *lymphovascular invasion, papillary thyroid carcinoma, radioactive iodine therapy, dose activity of I-131*

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## INTRODUCTION

There has been a steady increase in thyroid cancer incidence globally. In Europe, for example, it has been found that there has been a linear increase in incidence of thyroid cancer in Great Britain (1). This has led to a doubling of the number of cases diagnosed in Great Britain in the past 20 years. Across the Atlantic in continental United States, there has been a 2.4-fold increase in thyroid cancer incidence since 1973 to 2002 (2). In the local setting, there has been a recorded annual change of 0.4% and 1.6% in incidence rates in males and females, respectively (3).

The most common type of thyroid malignancy is papillary thyroid carcinoma (4). In addition to this,

papillary thyroid cancer incidence has been rapidly increasing worldwide in the past 15 years (5). A study by Bernstein et al. suggests that thyroid cancer is more indolent or aggressive in Filipinos because they tend to have more advanced cancer at diagnosis compared to non-Hispanic whites (6). In the same study, they found that Filipinos have a higher incidence of developing thyroid carcinoma compared to other ethnic groups. Considering these recent data, this is a problem locally.

A variety of recently used prognostic scoring systems take into consideration lymph node metastasis. This helps in pretreatment planning of the patient. Papillary thyroid carcinoma metastasizes through a different route from the follicular type of thyroid cancer. Instead of spreading hematogenously, papillary thyroid cancer metastasizes using the lymphatic route (7). Consequently, lymph node metastasis to proximal cervical nodes happens. It has been noted that lymph node metastasis poorly and independently affects disease-free survival of patients in papillary thyroid carcinoma (8). Histologically, lymphovascular invasion (LVI) is a predictor of lymph node metastasis in the carcinoma of the cervix (9). In colorectal cancer, LVI is a poor prognostic factor (2). Not surprisingly, LVI is also associated with cervical lymph node metastasis in papillary thyroid carcinoma (10).

In the study by Lim et al. (11), they retrospectively found that 36% (21 of 58) of patients with LVI in papillary thyroid microcarcinoma had ipsilateral central lymph node metastasis. In addition to this, they found out that LVI and a high MACIS (Metastasis, Age, Completeness of resection, Invasion, Size of tumor) score were predictive of contralateral cervical lymph node metastases. In another study by Miao et al. (12), it was revealed that 65% (93/143), 22% (32/143) and 18% (26/143) of patients with papillary thyroid cancer presenting with LVI had ipsilateral paratracheal, pretracheal and contralateral paratracheal lymph node metastasis, respectively. Kim et al. (10) reported that LVI was associated with lateral cervical lymph node metastasis in patients with papillary thyroid carcinoma. Koo et al. also found that contralateral cervical lymph node metastasis was significantly increased in patients diagnosed to have papillary thyroid carcinoma with LVI (13).

## GENERAL OBJECTIVE

To determine the association of lymphovascular invasion (LVI) with local cervical lymph node metastasis and distant metastasis among adult patients with papillary thyroid carcinoma.

## SPECIFIC OBJECTIVES

1. To determine demographics of patients with and without LVI among adult patients with papillary thyroid carcinoma
2. To determine the association of metastasis (local or distant) in patients with LVI among patients with papillary thyroid carcinoma
3. To determine the success rate of radioactive iodine treatment among patients with papillary thyroid carcinoma with and without LVI
4. To determine the association of dose activity and metastasis among patients with LVI and those patients without LVI
5. To determine the association of thyroglobulin levels in patients with and without LVI

## METHODOLOGY

*Study Design:*

This is a case control study.

*Study Population:*

Patients were recruited by reviewing baseline/post-RAI whole body scans done from January 2014 to December 2014 at a tertiary hospital. Their histopathologic reports and thyroglobulin levels were likewise reviewed. Their age, sex, radioactive iodine-131 treatment activity given and date, post-radioactive (baseline) I-131 treatment whole body scan and date, follow-up whole body I-131 scan report and date, and follow-up thyroglobulin levels and date were collected and tallied. Age was recorded as the patient's age stated at their post-thyroidectomy histopathologic reports, essentially the time the patient was diagnosed with papillary thyroid carcinoma. Included subjects were adult patients (at least 18 years old) with papillary thyroid carcinoma who underwent total thyroidectomy with histopathologic reports and underwent radioactive iodine ablation.

*Exclusion Criteria:*

Excluded patients were patients without follow-up I-131 whole body scan and/or thyroglobulin level monitoring, patients diagnosed with thyroid carcinoma other than papillary thyroid carcinoma, and patients diagnosed with another malignancy other than thyroid carcinoma. Patients were followed up for at least 6 months from the baseline/post-radioactive iodine treatment whole body scan.

*Operational Definitions:*

1. Case – patients diagnosed with papillary thyroid carcinoma with lymphovascular invasion on histopathologic report
2. Control – patients diagnosed with papillary thyroid carcinoma without lymphovascular invasion on histopathologic report
3. Lymphovascular invasion – positive or reported lymphovascular invasion in histopathology
4. High-dose radioactive iodine therapy – radioactive iodine therapy with a dose of at least 3700 Megabecquerels
5. Low-dose radioactive iodine therapy – radioactive iodine therapy with a dose of less than 3700 Megabecquerels
6. Elevated thyroglobulin – thyroglobulin level of greater than 2 nanograms per milliliter (ng/mL) or 2 micrograms per liter (ug/L)
7. Successful radioactive iodine treatment – negative non-physiological uptake on I-131 whole body scan and/or thyroglobulin levels less than 2 nanograms per milliliter (ng/mL) or 2 micrograms per liter (ug/L) on follow-up
8. Metastasis – presence of I-131 uptake on any part of the body other than physiologic tracer uptake on follow-up I-131 whole body scan

*Sample Size:*

Sample size was calculated for an unmatched case-control study with 95% confidence interval, 80% power, a ratio of 1:1 cases and controls and an expected frequency of recurrence in control group of 13.6%, to be able to detect a 5.5 Odds ratio. The 13.6% recurrence in control group was based on results of retrospective study undertaken by Kim et al (10). The sample size required was 54 subjects (27 controls and 27 cases).

The actual number of subjects recruited were 108 patients with papillary thyroid carcinoma who underwent thyroidectomy and radioactive iodine therapy with I-131 whole body scan with and without lymphovascular invasion.

*Statistical Analysis:*

Statistical analysis was performed using SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). Pearson chi-square, log regression test for categorical variables was used in the univariate analyses of the clinical characteristics. Variables with a $p$-value of less than 0.05 in the univariate analysis were included in multivariate logistic regression analysis.

## RESULTS

A total of 108 patients were included in this study. Forty seven (43.5%) subjects were positive for lymphovascular invasion (LVI). This consisted of 42 females and 5 males with a mean age of 41.85 years old. A significant association was seen with younger age of diagnosis and LVI. There was no significant association between gender and LVI.

Table 1. Demographics and baseline scan results

| | Lymphovascular Invasion (+) | Lymphovascular Invasion (-) | $p$ |
|---|---|---|---|
| Age | 41.85 ± 12.30 | 47.00 ± 12.06 | 0.03 |
| Gender | | | |
| Male | 5 (10.6%) | 6 (9.8%) | |
| Female | 42 (89.4%) | 55 (90.2%) | |
| Elevated Tg on follow-up | 14 | 7 | <0.0001 |
| LN metastasis on baseline | 16 | 17 | |
| Distant metastasis on baseline | 1 | 1 | 0.72 |
| Both LN and distant metastasis on baseline | 4 | 3 | |

A significant association was seen between elevated thyroglobulin on follow-up and presence of LVI. There was no significant association between LVI and metastasis on both baseline whole body scans.

There was also no significant association between LVI and metastasis on follow-up whole body scans. However, a high percentage (44.6%) of patients with LVI had metastasis.

On follow-up scans, presence of LVI was again not associated with metastasis despite the $p$-value of 0.07 nearing the 0.05 mark (Table 2).

Table 2. Follow-up

| | Lymphovascular Invasion (+) | Lymphovascular Invasion (-) |
|---|---|---|
| New metastasis on ff-up | 4 (9.1%) | 5 (11.1%) |
| Stable/Same on follow-up | 25 (56.8%) | 27 (60.0%) |
| Regression on ff-up | 6 (13.6%) | 0 |
| Resolution on ff-up | 9 (20.5%) | 13 (28.9%) |

$p = 0.07$

There was a significant association of resolution seen on follow-up scans in patients who received a dose activity of at least 3700 MBq regardless of presence or absence of LVI ($p = 0.02$). (Table 3)

Table 3. Dose activity and metastasis on follow-up scans in lymphovascular Invasion (+) and lymphovascular Invasion (-).

| Dose | New | Same | Regress | Resolved | $p$ |
|---|---|---|---|---|---|
| ≥ 3700 MBq | 1 (25.0%) | 21 (84.0%) | 6 (100%) | 6 (66.7%) | 0.02 |
| < 3700 MBq | 3 (75.0%) | 4 (16.0%) | 0 | 3 (33.3%) | |

On further stratification, a significant association was seen between resolution and giving at least 3700 MBq I-131 in follow-up scans ($p = 0.02$). (Table 4)

Table 4. Association of dose activity and metastasis among patients with lymphovascular invasion on follow-up scans and association of dose activity with metastasis in lymphovascular invasion (-) patients.

| | Dose Activity | Resolved | *p*-value |
|---|---|---|---|
| Lymphovascular invasion (+) | 3700 to <5550 MBq | 1 | 0.02 |
| | ≥ 5550 MBq | 5 | |
| Lymphovascular invasion (–) | 3700 to <5550 MBq | 4 | 0.009 |
| | ≥ 5550 MBq | 6 | |

A significant association was seen between metastasis and resolution on both baseline ($p$ = 0.003) and follow-up scans ($p$ = 0.009) in patients receiving at least 3700 MBq.

## DISCUSSION

No significant association was seen between lymphovascular invasion (LVI) and metastasis (locoregional lymph node or distant) on baseline and follow-up whole scans. This is contrary to what Kim et al. (10) reported between the association of cervical lymph node metastasis and LVI. Though no association was seen, this study tallied almost half (44.6%) of the patients with LVI were positive for metastasis in their baseline scans. Furthermore, although not significant ($p$ = 0.07), the association of LVI with metastasis on follow-up scans was nearing the 0.05 $p$-value.

There was a significant association between younger age at diagnosis and LVI. The mean age of patients with LVI was 41.85 years old compared to the mean age of patients without LVI which was 47 years old. This suggests a more aggressive disease in younger patients.

All the patients with elevated thyroglobulin levels on follow-up were positive for LVI. This demonstrated a significant association in patients with elevated thyroglobulin levels on follow-up and presence of LVI. LVI, then, may be considered a marker for elevated thyroglobulin levels on follow-up monitoring post thyroidectomy.

Success rate of treatment was 80% (36/45) in patients with LVI-negative histopathologic reports. In patients with LVI-positive histopathologic reports, the success rate was 63% (28/44). Knowing that varying dose activities are given to these patients, it may be a good idea to increase the dose activity given to these patients with LVI. This is because when subdivided between high-dose and low-dose treatment, a significant association was seen between disease resolution on follow-up scans in patients who received high-dose treatment. This is further validated when on further stratification of high-dose activity between 3700 MBq to less than 5550 MBq and at least 5550 MBq, a significant association was seen between disease resolution on follow-up scans only in patients with LVI.

No significant association was seen on disease resolution on baseline scans. This is expected as baseline/post-radioactive iodine treatment body scans are mostly requested in our institution 2 to 3 days after treatment which is shorter than the half-life of I-131.

For patients without LVI, a significant association was seen between disease resolution on both baseline and follow-up scans and higher dose activity (at least 3700 MBq). However, in these patients without lymphovascular invasion, 5 patients developed new metastasis. Histopathologic reports were further reviewed in these patients. All 5 patients had surgical margins free of tumor. No blood vessel invasion was seen. All of them however, had a tumor larger than 1 cm with 1.1 cm as the smallest and 2.4 cm as

the largest. The patient who had a 1.1 cm tumor was reported to have multifocal tumors (4 foci). All the rest had a single focus. Furthermore, all of the 5 patients were females and above 45 years old. Only 1 patient was below 50 years old. As Davies et al. mentioned, being Filipino may be a factor for a more advanced and essentially aggressive disease (2).

## CONCLUSION

There is a significant association between the presence of lymphovascular invasion (LVI) and elevated thyroglobulin levels on follow-up. Likewise, there is a significant association between LVI and dose activity with resolution of thyroid remnant, locoregional lymph node and distant metastasis.

Relatively young age is associated with LVI. Gender is not associated with LVI. Higher dose activity received is associated with metastasis resolution on follow-up whole body scans. For LVI-positive patients, a higher dose activity is also associated with metastasis resolution on follow-up whole body scans. For LVI-negative patients, a significant association is seen between metastasis resolution on baseline and follow-up whole body scans and those who received high dose treatment.

Limitations of the study stem from its study design. Being a case control study, it could not accurately estimate the risk of patient metastasis unlike cohort studies. Furthermore, no standard therapy was done in our subjects. Patients had different attending physicians handling them such as endocrinologists and nuclear medicine physicians.

Based on the results of this study, it is recommended to give at least 3700 MBq in patients with LVI. Also, pre-radioactive iodine therapy whole body scan may be useful in patients with and without LVI. This will help in tailoring the dose activity to be given to the patient if ever metastasis is seen on pre-radioactive iodine therapy scans. Though known to all astute clinicians, it is also recommended to be more suspicious of metastasis in female Filipino patients with or without LVI aged 45 years old and above.

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