Lymph node Ratio is Superior to AJCC N Stage for Predicting Recurrence in Papillary Thyroid Carcinoma

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Abstract

Objective: Recently, lymph node ratio (LNR) has emerged as an alternative to American Joint Committee on Cancer (AJCC) N stage, with superior prognostic value. The utility of LNR in Middle Eastern Papillary thyroid carcinoma (PTC) remains unknown. Therefore, we retrospectively analyzed a large cohort of 1407 PTC patients for clinico-pathological associations of LNR.

Methods: Receiver operating characteristics (ROC) curve was used to determine the cut-off for LNR. We also performed multivariate logistic regression analysis to determine whether LNR or AJCC N stage was superior in predicting recurrence in PTC.

Results: Based on ROC curve analysis, a cut-off of 0.15 was chosen for LNR. High LNR was significantly associated with adverse clinico-pathological characteristics such as male sex, extrathyroidal extension, lymphovascular invasion, multifocality, bilateral tumors, T4 tumors, lateral lymph node (N1b) involvement, distant metastasis, advanced tumor stage, ATA high risk category and tumor recurrence. On multivariate analysis, we found that LNR was a better predictor of tumor recurrence than AJCC N stage (Odds ratio: 1.96 vs. 1.30; p value: 0.0184 vs. 0.3831). We also found that LNR combined with TNM stage and ATA risk category improved the prediction of recurrence-free survival, compared to TNM stage or ATA risk category alone.

Conclusions: The present study suggests LNR is an independent predictor of recurrence in Middle Eastern PTC. Integration of LNR with 8th edition AJCC TNM staging system and ATA risk stratification will improve the accuracy to predict recurrence in Middle Eastern PTC and help in tailoring treatment and surveillance strategies in these patients.
Introduction

Papillary thyroid carcinoma (PTC) is the commonest subtype of thyroid cancer, accounting for 80-90% of all thyroid cancers, and is generally associated with favorable outcome 1, 2. The incidence of PTC has increased significantly in recent years 3, 4. In Saudi Arabia, PTC is very common among females and ranks second, after breast cancer 5. Although PTC has favorable outcome, 3-10% of patients demonstrated recurrent disease within the first decade after treatment 6, 7. Accurate PTC staging is an important process to help clinicians pursue the best therapeutic options for their patients.

American Joint Committee on Cancer (AJCC) TNM staging system is the most commonly used staging system for thyroid cancer. AJCC nodal (N) stage in PTC is subdivided based on the anatomical location of lymph node (LN) metastasis, being classified as central LN (N1a) or lateral LN (N1b) metastasis 8. Although it has been reported that LN involvement can impact patient’s prognosis and increase the risk of recurrence as well as distant metastasis 9-14, the association of N stage with clinico-pathological markers and prognosis has not been fully explored in PTC from Middle Eastern ethnicity.

In addition, using N stage classification only might underestimate the significance and the extent of burden of the disease since it is based solely on anatomical location of LN metastasis. An additional emerging prognostic factor in PTC is the lymph node ratio (LNR) 15-18. The LNR, which is defined as the number of LNs showing metastatic
deposits divided by the number of LN resected, is suggested to be a superior prognostic variable, better reflecting tumor burden and recurrence prediction \(^{19-22}\).

Disease recurrence is the most relevant oncologic outcome in PTC since mortality rate from PTC is very low \(^{23, 24}\). To date, whether the LNR works better than the 8\(^{th}\) AJCC N staging in predicting recurrence in Middle Eastern PTC remains unknown. In this study, we retrospectively enrolled 1407 PTC patients with clinico-pathological and follow-up information and compared the effectiveness of AJCC 8\(^{th}\) edition N staging and LNR in predicting the recurrence of PTC patients from Middle Eastern ethnicity.
Materials and Methods

Patient selection

One thousand five-hundred and fifteen consecutive unselected PTC patients diagnosed between 1988 and 2018 at King Faisal Specialist Hospital and Research Centre (Riyadh, Saudi Arabia) were available to be included in the study. Patients in whom regional LN could not be evaluated (Nx) were excluded from the study (n = 108). A total of 1407 PTC cases were included for analysis. Cases were identified based on clinical history followed by fine needle aspiration cytology for confirmation. The Institutional Review Board, King Faisal Specialist Hospital and Research Centre, approved this study and the Research Advisory Council (RAC) provided waiver of consent under project RAC # 2211168 and RAC # 2110031.

Clinico-pathological data

Baseline clinico-pathological data were collected from case records and have been summarized in Table 1. Based on the American Thyroid Association (ATA) guidelines, tall cell, hobnail, columnar cell, diffuse sclerosing and insular variants were classified as aggressive variants, whereas classical and follicular variants were classified as non-aggressive variants. Staging of PTC was performed using the eighth edition of AJCC staging system. Only structural recurrence (local, regional or distant) was considered for
analysis. Recurrence was defined as any newly detected tumor (local or distant) or metastatic regional lymph node (LN) based on ultrasound and/or imaging studies in patients who had been previously free of disease following initial treatment. Radioactive iodine (RAI) refractory disease and risk categories were defined based on 2015 ATA guidelines.

**Lymph node ratio (LNR) cut-off**

LNR was defined as the number of metastatic LNs divided by the number of LNs resected. To determine the cut-off value for LNR, we used the receiver operating characteristic (ROC) curve analysis. Using recurrence-free survival as the outcome, we calculated the area under curve (AUC), sensitivity, specificity and 95% confidence intervals. We found that LNR of 0.15 was related to tumor recurrence with AUC of 0.668, sensitivity of 69% and specificity of 59% (p < 0.001; Figure 1). Hence, a cut-off of 0.15 was chosen for analysis of clinico-pathological associations of LNR.

**BRAF and TERT mutation analysis**

*BRAF* and *TERT* mutation data was assessed in our laboratory by Sanger sequencing and has been published by us previously.

**PD-L1 immunohistochemistry**

PD-L1 immunohistochemical staining and analysis was performed by us previously in PTC. Briefly, tissue microarray slides were processed and stained manually. Primary
antibody against PD-L1 (E1L3N, 1:50 dilution, pH 9.0, Cell Signaling Technology, Danvers, MA) was used. A membranous and/or cytoplasmic staining was observed. Only the membrane staining was considered for scoring. PD-L1 was scored as described previously. Briefly, the proportion of positively stained cells was calculated as a percentage for each core and the scores were averaged across two tissue cores from the same tumor to yield a single percent staining score representing each cancer patient. For the purpose of statistical analysis, the scores were dichotomised. Cases showing expression level of \( \geq 5\% \) were classified as over-expression and those with less than 5\% as low expression.

**Follow-up and Study endpoint**

Patients were regularly followed by both physical examinations and imaging studies to identify tumor recurrence. The median follow-up was 9.2 years (range 1.0 – 30.1 years). Recurrence-free survival (RFS) was defined as the time (in months) from date of initial surgery to the occurrence of any tumor recurrence (local, regional or distant). In case of no recurrence, date of last follow-up was the study endpoint for RFS.

**Statistical analysis**

The associations between clinico-pathological variables was performed using contingency table analysis and Chi square tests. Cut-off for LNR was determined using the ROC curve. Logistic regression was used for multivariate analysis. Two-sided tests were used for statistical analyses with a limit of significance defined as p value < 0.05. All data analyses, except ROC curve analysis, were performed using the JMP14.0 (SAS...
Institute, Inc., Cary, NC) software package. ROC curve analysis was performed using MedCalc software, version 10.4.7.0 for Windows (MedCalc, Ostend, Belgium).

Results

Patient and tumor characteristics

Median age of the study cohort was 37.7 years (range = 6.0 – 88.0 years), with a male:female ratio of 1:3.2. Classical variant PTC was the predominant histologic subtype, accounting for 67.3% (948/1407) of all cases, followed by follicular variant (17.0%; 239/1407) and tall cell variant 9.0% (126/1407). Extrathyroidal extension was noted in 44.1% (621/1407) of cases and lymphovascular invasion in 21.2% (298/1407). 49.6% (698/1407) of PTCs were multifocal and 32.5% (457/1407) were bilateral. Tumor recurrence was noted in 19.5% (275/1407) of the entire cohort (Table 1). The median time to first recurrence from initial surgery in our cohort was 2.6 years (range 0.6 – 19.8 years). The median number of LNs removed was 15 with the following N stage distribution: N0 (47.0%; 661/1407), N1a (14.6%; 206/1407), and N1b (38.4%; 540/1407) (Table 1). BRAF mutation was noted in 55.6% (768/1381) PTCs and TERT mutation was seen in 13.9% (181/1305). Both BRAF and TERT mutation data were available for 1299 patients in our cohort. Co-existence of BRAF and TERT mutation was noted in 10.5% (136/1299) of cases.

Incidence and clinico-pathological associations of recurrence in PTC

Tumor recurrence was noted in 19.5% (275/1407) of PTCs during follow-up. Recurrence was significantly associated with adverse clinico-pathological parameters,
such as age ≥ 55 years (p < 0.0001), male sex (p < 0.0001), extrathyroidal extension (p < 0.0001), bilateral tumors (p < 0.0001), T4 tumors (p < 0.0001), LN metastasis (p < 0.0001), distant metastasis (p < 0.0001), advanced tumor stage (p < 0.0001), RAI refractory disease (p < 0.0001) and ATA high risk category (p < 0.0001). On further division of N1 tumors into N1a and N1b, we found that 31.1% (168/540) of N1b tumors developed recurrence, compared to 17.0% (35/206) of N1a tumors. The difference in recurrence rate between N1a and N1b tumors was statistically significant (p = 0.0001) (Table 2).

**Clinico-pathological associations of LNR in PTC**

Using a cut-off of 0.15, 44.8% (631/1407) of tumors had high LNR. Tumors exhibiting a high LNR were significantly associated with male sex (p = 0.0019), extrathyroidal extension (p < 0.0001), lymphovascular invasion (p = 0.0034), multifocality (p < 0.0001), bilateral tumors (p < 0.0001), T4 tumors (p < 0.0001), N1b (p < 0.0001), distant metastasis (p = 0.0006), advanced tumor stage (p = 0.0246), RAI refractory disease (p < 0.0001) and ATA high risk category (p < 0.0001). We also found a significant association with tumor recurrence (p < 0.0001). Interestingly, high LNR was associated with *BRAF* mutation (p < 0.0001) and PD-L1 expression (p = 0.0031) (Table 3).

**LNR is a better predictor of tumor recurrence than AJCC N stage**

Since high LNR was associated with tumor recurrence, we sought to determine whether it could be used an independent predictor of recurrence. Using multivariate logistic regression analysis, we found high LNR to be an independent predictor of recurrence.
LNR combined with TNM stage and ATA risk category as a predictor of recurrence-free survival

We next sought to analyze whether LNR combined with TNM stage and ATA risk category could better predict RFS, compared to either of them alone. On multivariate Cox proportional hazards model, we found that compared to TNM stage alone, the hazard ratios of corresponding stage combined with LNR was higher (Table 5). Similarly, the hazard ratios of ATA risk category combined with LNR was higher, compared to the corresponding ATA risk category alone (Table 6). This suggests that combining LNR with TNM stage or ATA risk category was a better predictor of RFS compared to either of them alone.
Discussion

Cancer recurrence remains a major challenge for PTC patients. It is clinically important to identify markers that can accurately predict recurrence. Predicting tumor recurrence is needed to tailor the initial treatment and follow-up intensity. In this study, we first determined the tumor recurrence rate to be 19.5% (275/1407) in Middle Eastern PTC. This recurrence rate is relatively high\(^2\) and highlights the urgent need to establish an accurate model to predict recurrence in PTC patients from Middle Eastern ethnicity. Interestingly, our cohort also presented with more aggressive disease, as evidenced by a high rate of aggressive variants (15.7%), multifocality (49.6%), extrathyroidal extension (44.1%) and a lower age at presentation (median, 38 years). This probably reflects the inherent aggressive nature of PTC in this ethnicity, as evidenced by other studies from this region, which also found a relatively high rate of aggressive variants\(^3\), multifocality\(^4\),\(^5\), extrathyroidal extension\(^2\),\(^3\) and a low median age at diagnosis\(^6\).\(^7\). However, it could also be partially attributed to the fact that ours is the foremost tertiary care center in the region and most advanced diseases are referred to our hospital from all over Saudi Arabia.

Tumor recurrence was significantly associated with advanced T stage (\(p < 0.0001\)). Surprisingly 17.6% (99/564) of pT1 tumors exhibited tumor recurrence, which is relatively higher in comparing to other studies where recurrence rate in T1 is rare\(^8\).
Comparing within AJCC N stage subgroups, tumor recurrence was found to be significantly more common in patients with N1b stage (31.1%, 168/540) as against patients with N1a (17.0%, 35/206) and N0 (10.9%, 72/661), as expected. Although the 8th edition of AJCC TNM staging is commonly used to predict patient’s outcome, it has some limitations. Patients with PTC and LN metastasis are staged according to the presence or absence of LN metastasis in anatomic compartments. The extent of the disease is not considered in this staging system. There is growing evidence showing the value of considering the extent of LN metastasis in PTC prognosis. The American Thyroid Association (ATA) risk stratification system now considers the size and number of LN metastasis as an important factor in risk stratification.

Recently, more tailored risk stratification using LNR was proposed as a more reliable prognosticator of recurrence in PTC. Recent investigations of LNR in PTC have suggested that it has prognostic significance in both the central as well as lateral LN metastasis and maybe superior to conventional AJCC staging. Others have suggested integration of LNR to the current staging system to improve prediction of recurrence in patients with PTC. For Middle Eastern PTC, the use of LNR as a predictive tool for recurrence has not previously been analyzed. In this study, using a cut off of 0.15 for LNR, we were able to identify a subset of Middle Eastern PTC patients at high risk of tumor recurrence and that LNR was positively associated with adverse clinico-pathological characteristics, such as male gender, multifocality, larger tumor size, extrathyroidal extension, bilateral tumors and RAI-refractiveness. We also noted a positive correlation between LNR and BRAF mutations as well as PD-L1 protein.
overexpression, which we previously have shown to have negative impact on Middle Eastern PTC\textsuperscript{26, 47}.

Interestingly, LNR of more than 0.15 was a strong independent predictor of tumor recurrence (Odds ratio = 1.96; 95\% confidence interval = 1.12 – 3.43; \(p = 0.0184\)). Patients with LNR more than 0.15 exhibited a 2-fold higher risk of recurrence, while patient with N1 (using AJCC N staging) showed a 1.3-fold high risk of recurrence, suggesting that LNR was a better predictor of recurrence than the AJCC N stage. The fact that higher LNR increased the HR of the same stage tumor especially for TNM stage I (Table 5), is strong indication of LNR predictive power of recurrence even in early stage. Also patients with high risk ATA with LNR \(\geq 0.15\) had a much higher HR compared to high risk ATA category alone (6.08 vs. 4.67; Table 6), further strengthens the importance of LNR as a predictor of recurrence. This is clinically very important since it indicates that LNR is the most suitable and valuable predictor for recurrence in PTC patients of Middle Eastern ethnicity and suggests that adding LNR to 8\textsuperscript{th} AJCC TNM staging and ATA risk stratification system should be considered by clinicians to increase the accuracy of predicting PTC recurrence in this population.

Our study included a large sample size from Middle Eastern population allowing for adequate multivariable adjustment for patient and treatment characteristics. Also, this study is from a single institute, which helped in providing accurate and homogenous information such as gene mutations, type of therapy and length of follow-up. Despite the strength of this study, it is limited by its retrospective nature which could cause selection bias. Also this study was conducted on PTC from a specific ethnicity and therefore
further larger multicenter studies from other ethnicities are encouraged to make
generalizable conclusions.

In conclusion, the present study suggests LNR is an independent predictor of
recurrence in Middle Eastern PTC. Integration of LNR with 8th edition AJCC TNM
staging system and ATA risk stratification will improve the accuracy to predict
recurrence in Middle Eastern PTC and help in tailoring treatment and surveillance
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Figure legend

Figure 1: Receiver operating characteristic (ROC) curve for lymph node ratio (LNR). Tumors with LNR of 0.15 predicted PTC recurrence with a sensitivity of 69%, specificity of 59%, and area under cover (AUC) of 0.668 (p < 0.001).
Table 1. Patient characteristics of the study cohort

| Characteristic                                | Overall cohort (n = 1407) |
|-----------------------------------------------|---------------------------|
| **Age at diagnosis (years)**                  |                           |
| Median (range)                                | 37.7 (6.0 – 88.0)         |
| < 55                                          | 1160 (82.4)               |
| ≥ 55                                         | 247 (17.6)                |
| **Gender**                                   |                           |
| Male                                          | 333 (23.7)                |
| Female                                        | 1074 (76.3)               |
| **Histologic subtype**                       |                           |
| Classical variant                             | 948 (67.3)                |
| Follicular variant                            | 239 (17.0)                |
| Tall cell variant                             | 126 (9.0)                 |
| Other variants                                | 94 (6.7)                  |
| **Extrathyroidal extension**                  |                           |
| Present                                       | 621 (44.1)                |
| Absent                                        | 786 (55.9)                |
| **Lymphovascular invasion**                   |                           |
| Present                                       | 298 (21.2)                |
| Absent                                        | 1109 (78.8)               |
| **Tumor focality**                            |                           |
| Unifocal                                      | 709 (50.4)                |
| Multifocal                                    | 698 (49.6)                |
| **Tumor laterality**                          |                           |
| Unilaterial                                    | 950 (67.5)                |
| Bilateral                                     | 457 (32.5)                |
| **Surgical margin**                           |                           |
| Positive                                      | 387 (27.5)                |
| Negative                                      | 1020 (72.5)               |
| **pT**                                        |                           |
| T1                                            | 564 (40.2)                |
| T2                                            | 452 (32.2)                |
| T3                                            | 271 (19.3)                |
| T4                                            | 117 (8.3)                 |
| **Regional LN metastasis**                    |                           |
| N0                                            | 661 (47.0)                |
| N1a                                           | 206 (14.6)                |
| N1b                                           | 540 (38.4)                |
| **pM**                                        |                           |
| M0                                            | 1332 (94.7)               |
| M1                                            | 75 (5.3)                  |
| **TNM Stage**                                 |                           |
| I                                             | 1176 (83.7)               |
| II                                            | 156 (11.1)                |
| III                                           | 22 (1.6)                  |
| IV                                            | 51 (3.6)                  |
| **BRAF mutation**                             |                           |
| Present                                       | 768 (54.6)                |
| Absent                                        | 613 (44.6)                |
| Unknown                                       | 26 (1.8)                  |
| **TERT mutation**                             |                           |
| Present                                       | 181 (12.9)                |
|                                | Number | Percentage |
|--------------------------------|--------|------------|
| Absent                         | 1124   | 79.9       |
| Unknown                        | 102    | 7.2        |
| **PD-L1 IHC**                  |        |            |
| Positive                       | 435    | 32.7       |
| Negative                       | 896    | 67.3       |
| **Initial surgery**            |        |            |
| Lobectomy                      | 220    | 15.6       |
| Total thyroidectomy alone      | 374    | 26.5       |
| Total thyroidectomy with central neck dissection | 813 | 57.9 |
| **RAI given**                  |        |            |
| Yes                            | 1185   | 84.2       |
| No                             | 222    | 15.8       |
| **RAI Refractory**             |        |            |
| Yes                            | 244    | 20.6       |
| No                             | 941    | 79.4       |
| **Recurrence**                 |        |            |
| Yes                            | 275    | 19.5       |
| No                             | 1132   | 80.5       |
| **ATA risk category**          |        |            |
| Low                            | 231    | 16.4       |
| Intermediate                   | 460    | 32.7       |
| High                           | 716    | 50.9       |
Table 2. Clinico-pathological associations of recurrence in papillary thyroid carcinoma

|                                | Total No. | Recurrence present No. | Recurrence absent No. | p value |
|--------------------------------|-----------|------------------------|-----------------------|---------|
|                                |           | %                      | %                     |         |
| Total                          | 1407      | 275 (19.5%)            | 1132 (80.5%)          |         |
| Age at surgery (years)         |           |                        |                       |         |
| < 55                           | 1160      | 188 (68.4%)            | 972 (85.9%)           | < 0.0001|
| ≥ 55                           | 247       | 87 (31.6%)             | 160 (14.1%)           |         |
| Gender                         |           |                        |                       |         |
| Male                           | 333       | 93 (28.3%)             | 240 (14.1%)           | < 0.0001|
| Female                         | 1074      | 182 (16.9%)            | 892 (83.1%)           |         |
| Histologic subtype             |           |                        |                       |         |
| Classical variant              | 948       | 206 (74.9%)            | 742 (65.6%)           | 0.0026  |
| Follicular variant             | 239       | 28 (11.9%)             | 211 (88.1%)           |         |
| Tall cell variant              | 126       | 26 (20.6%)             | 100 (79.4%)           | 18.6    |
| Other variants                 | 94        | 15 (16.1%)             | 79 (83.9%)            | 7.0     |
| Extrathyroidal extension       |           |                        |                       |         |
| Present                        | 621       | 185 (67.3%)            | 436 (32.7%)           | < 0.0001|
| Absent                         | 786       | 90 (11.6%)             | 696 (88.4%)           |         |
| Lymphovascular invasion        |           |                        |                       |         |
| Present                        | 298       | 57 (19.5%)             | 241 (80.5%)           | 0.8374  |
| Absent                         | 1109      | 218 (19.7%)            | 891 (80.3%)           |         |
| Tumor focality                 |           |                        |                       |         |
| Unifocal                       | 698       | 125 (18.1%)            | 573 (81.9%)           | 0.1242  |
| Multifocal                     | 709       | 150 (21.0%)            | 559 (79.0%)           |         |
| Tumor laterality               |           |                        |                       |         |
| Unilateral                     | 950       | 154 (16.4%)            | 796 (83.6%)           | < 0.0001|
| Bilateral                      | 457       | 121 (26.5%)            | 336 (73.5%)           |         |
| pT                              |           |                        |                       |         |
| T1                              | 564       | 99 (17.5%)             | 465 (82.5%)           | < 0.0001|
| T2                              | 452       | 63 (14.0%)             | 389 (86.0%)           |         |
| T3                              | 271       | 59 (21.8%)             | 212 (78.2%)           | 18.8    |
| T4                              | 117       | 53 (45.3%)             | 64 (54.7%)            | 5.7     |
| pN                              |           |                        |                       |         |
| N0                              | 661       | 72 (10.9%)             | 589 (90.1%)           | < 0.0001|
| N1a                             | 206       | 35 (16.9%)             | 171 (83.1%)           |         |
| N1b                             | 540       | 168 (31.1%)            | 372 (68.9%)           |         |
| LN ratio                        |           |                        |                       |         |
| ≥ 0.15                         | 631       | 184 (29.1%)            | 447 (70.9%)           | < 0.0001|
| < 0.15                         | 776       | 91 (11.8%)             | 685 (88.2%)           |         |
| pM                              |           |                        |                       |         |
| M0                              | 1332      | 225 (16.9%)            | 1107 (83.1%)          | < 0.0001|
| M1                              | 75        | 50 (66.7%)             | 25 (33.3%)            | 2.2     |
| TNM Stage                       |           |                        |                       |         |
| I                               | 1176      | 174 (14.9%)            | 1001 (85.1%)          | < 0.0001|
| II                              | 156       | 66 (42.1%)             | 90 (57.9%)            | 8.0     |
| III                             | 22        | 6 (27.3%)              | 16 (72.7%)            | 1.4     |
| IV                              | 51        | 28 (54.9%)             | 23 (45.1%)            | 2.0     |
| BRAF mutation                   |           |                        |                       |         |
| Present                         | 768       | 160 (20.9%)            | 608 (80.1%)           | 0.1323  |
| Absent                          | 613       | 108 (17.5%)            | 505 (82.5%)           |         |
| TERT mutation                   |           |                        |                       |         |
|                          | Present | Absent | PD-L1 IHC | RAI Refractory | ATA risk category |
|--------------------------|---------|--------|-----------|----------------|-------------------|
|                          | 181     | 1124   | 435       | 896            | 231               |
| Present                  | 13.9    | 86.1   | 32.7      | 67.3           | 16.4              |
| Absent                   | 85      | 175    | 111       | 152            | 12                |
| PD-L1 IHC                | 96      | 949    | 324       | 744            | 47                |
| Positive                 | 32.7    | 67.3   | 42.2      | 57.8           | 4.4               |
| Negative                 | 85      | 175    | 111       | 152            | 12                |
| PD-L1 IHC                | 96      | 949    | 324       | 744            | 47                |
| RAI Refractory           | 32.7    | 67.3   | 42.2      | 57.8           | 4.4               |
| Yes                      | 244     | 20.6   | 155       | 109            | 219               |
| No                       | 941     | 79.4   | 89        | 413            | 19.3              |
| ATA risk category        | 32.7    | 67.3   | 42.2      | 57.8           | 4.4               |
| Low                      | 244     | 20.6   | 155       | 109            | 219               |
| Intermediate             | 460     | 32.7   | 47        | 17.1           | 413               |
| High                     | 716     | 50.9   | 216       | 78.5           | 500               |
| ATA risk category        | 32.7    | 67.3   | 42.2      | 57.8           | 4.4               |
Table 3. Clinico-pathological associations of lymph node ratio (LNR) in papillary thyroid carcinoma

|                                  | Total | LNR ≥ 0.15 | LNR < 0.15 | p value |
|----------------------------------|-------|------------|------------|---------|
|                                  | No.   | %          | No.        | %       |         |
| Total                            | 1407  | 631        | 776        | 55.2    |         |
| Age at surgery (years)           |       |            |            |         |         |
| < 55                             | 1160  | 82.4       | 527        | 83.5    | 0.3391  |
| ≥ 55                             | 247   | 17.6       | 104        | 16.5    | 143     | 18.4    |
| Gender                           |       |            |            |         |         |
| Male                             | 333   | 23.7       | 174        | 27.6    | 159     | 20.5    | 0.0019  |
| Female                           | 1074  | 76.3       | 457        | 72.4    | 617     | 79.5    |         |
| Histologic subtype               |       |            |            |         |         |
| Classical variant                | 948   | 67.3       | 483        | 76.6    | 465     | 59.9    | < 0.0001|
| Follicular variant               | 239   | 17.0       | 48         | 7.6     | 191     | 24.6    |         |
| Tall cell variant                | 126   | 9.0        | 60         | 9.5     | 66      | 8.5     |         |
| Other variants                   | 94    | 6.7        | 40         | 6.3     | 54      | 7.0     |         |
| Extrathyroidal extension         |       |            |            |         |         |
| Present                          | 621   | 44.1       | 379        | 60.1    | 242     | 31.2    | < 0.0001|
| Absent                           | 786   | 55.9       | 252        | 39.9    | 534     | 68.8    |         |
| Lymphovascular invasion          |       |            |            |         |         |
| Present                          | 298   | 21.2       | 156        | 24.7    | 142     | 18.3    | 0.0034  |
| Absent                           | 1109  | 78.8       | 475        | 75.3    | 634     | 81.7    |         |
| Tumor focality                   |       |            |            |         |         |
| Unifocal                         | 698   | 49.6       | 272        | 43.1    | 426     | 54.9    | < 0.0001|
| Multifocal                       | 709   | 50.4       | 359        | 56.9    | 350     | 45.1    |         |
| Tumor laterality                 |       |            |            |         |         |
| Unilateral                       | 950   | 67.5       | 370        | 58.6    | 580     | 74.7    | < 0.0001|
| Bilateral                        | 457   | 32.5       | 261        | 41.4    | 196     | 25.3    |         |
| pT                               |       |            |            |         |         |
| T1                               | 564   | 40.2       | 219        | 34.8    | 345     | 44.6    | < 0.0001|
| T2                               | 452   | 32.2       | 209        | 33.2    | 243     | 31.4    |         |
| T3                               | 271   | 19.3       | 131        | 20.8    | 140     | 18.1    |         |
| T4                               | 117   | 8.3        | 71         | 11.3    | 46      | 5.9     |         |
| pN                               |       |            |            |         |         |
| N0                               | 661   | 47.0       | 0          | 0.0     | 661     | 85.2    | < 0.0001|
| N1a                              | 206   | 14.6       | 174        | 27.6    | 32      | 4.1     |         |
| N1b                              | 540   | 38.4       | 457        | 72.4    | 83      | 10.7    |         |
| pM                               |       |            |            |         |         |
| M0                               | 1332  | 94.7       | 583        | 92.4    | 749     | 96.5    | 0.0006  |
| M1                               | 75    | 5.3        | 48         | 7.6     | 27      | 3.5     |         |
| TNM Stage                        |       |            |            |         |         |
| I                                | 1176  | 83.7       | 506        | 80.4    | 670     | 86.3    | 0.0246  |
| II                               | 156   | 11.1       | 86         | 13.7    | 70      | 9.0     |         |
| III                              | 22    | 1.6        | 12         | 1.9     | 10      | 1.3     |         |
| IV                               | 51    | 3.6        | 25         | 4.0     | 26      | 3.4     |         |
| BRAF mutation                    |       |            |            |         |         |
| Present                          | 768   | 55.6       | 388        | 62.7    | 380     | 49.9    | < 0.0001|
| Absent                           | 613   | 44.4       | 231        | 37.3    | 382     | 50.1    |         |
| TERT mutation                    |       |            |            |         |         |
| Present                          | 181   | 13.9       | 92         | 15.7    | 89      | 12.4    | 0.0934  |
| Absent                           | 1124  | 86.1       | 496        | 84.3    | 628     | 87.6    |         |
| PD-L1 IHC                        |       |            |            |         |         |
| Positive                         | 435   | 32.7       | 222        | 36.9    | 213     | 29.2    | 0.0031  |
|                  |     |     |     |     |     |     |
|------------------|-----|-----|-----|-----|-----|-----|
|                  |   896 | 67.3 | 380 | 63.1 | 516 | 70.8 |
| **RAI Refractory** |     |     |     |     |     |     |
| Yes              | 244 | 20.6 | 155 | 27.2 | 89  | 14.5 |
|                  |     |     |     |     |     |     |
| No               | 941 | 79.4 | 414 | 72.8 | 527 | 85.5 |
| **Recurrence**   |     |     |     |     |     |     |
| Yes              | 275 | 19.6 | 184 | 29.2 | 91  | 11.7 |
|                  |     |     |     |     |     |     |
| No               | 1132| 80.4 | 447 | 70.8 | 685 | 88.3 |
| **ATA risk category** |     |     |     |     |     |     |
| Low              | 231 | 16.4 | 1   | 0.2  | 230 | 29.6 |
|                  |     |     |     |     |     |     |
| Intermediate     | 460 | 32.7 | 226 | 35.8 | 234 | 30.2 |
|                  |     |     |     |     |     |     |
| High             | 716 | 50.9 | 404 | 64.0 | 312 | 40.2 |
Table 4. Multivariate logistic regression analysis for predictors of recurrence in papillary thyroid cancer

| Clinico-pathological variables | Univariate | Multivariate |
|-------------------------------|------------|--------------|
|                               | Odds ratio | 95% Confidence interval | p-value | Odds ratio | 95% Confidence interval | p-value |
| Age ≥ 55 years (vs. < 55 years) | 2.81       | 2.07 – 3.81 | < 0.0001 | 2.56       | 1.74 – 3.77 | < 0.0001 |
| Sex Male (vs. Female)          | 1.90       | 1.42 – 2.53 | < 0.0001 | 1.52       | 1.11 – 2.09 | 0.0094  |
| Histology Aggressive variants (vs. non-aggressive variants) | 0.93 | 0.65 – 1.35 | 0.7114 |
| Tumor laterality Bilateral (vs. unilateral) | 1.86 | 1.42 – 2.44 | < 0.0001 | 1.29       | 0.95 – 1.74 | 0.1012  |
| Tumor focality Multifocal (vs. Unifocal) | 1.23 | 0.94 – 1.60 | 0.1248 |
| Extrathyroidal extension Present (vs. Absent) | 3.28 | 2.48 – 4.34 | < 0.0001 | 1.89       | 1.38 – 2.59 | < 0.0001 |
| Lymphovascular invasion Present (vs. Absent) | 0.97 | 0.70 – 1.34 | 0.8378 |
| pT T3-4 (vs. T1-2) | 2.14 | 1.62 – 2.82 | < 0.0001 | 1.48       | 1.08 – 2.02 | 0.0154  |
| Distant metastasis Present (vs. absent) | 9.84 | 5.96 – 16.24 | < 0.0001 | 7.49       | 4.02 – 13.94 | < 0.0001 |
| TNM stage III-IV (vs. I-II) | 3.96 | 2.45 – 6.41 | < 0.0001 | 0.41       | 0.20 – 0.85 | 0.0170  |
| LN metastasis Present (vs. absent) | 3.05 | 2.28 – 4.10 | < 0.0001 | 1.30       | 0.72 – 2.35 | 0.3831  |
| LN ratio ≥ 0.15 (vs. < 0.15) | 3.09 | 2.35 – 4.09 | < 0.0001 | 1.96       | 1.12 – 3.43 | 0.0184  |
Table 5. Univariate and multivariate analyses of baseline variables for recurrence-free survival with the TNM staging system.

|                      | Univariate                  | Multivariate                |
|----------------------|-----------------------------|-----------------------------|
|                      | HR (95% CI)                 | p value                     |
|                      |                             | HR (95% CI)                 | p value |
| **8th TNM**          |                             |                             |
| I                    | reference                   | reference                   |
| II                   | 3.985 (2.997 – 5.300)       | < 0.0001                    |
|                      |                             | 4.250 (2.613 – 6.912)       | < 0.0001 |
| III                  | 3.030 (1.342 – 6.843)       | 0.0080                      |
|                      |                             | 3.103 (1.180 – 8.165)       | 0.0220  |
| IV                   | 7.923 (5.286 – 11.873)      | < 0.0001                    |
|                      |                             | 7.320 (3.759 – 14.252)      | < 0.0001 |
| **8h TNM with LNR**  |                             |                             |
| I with low LNR       | reference                   | reference                   |
| II with low LNR      | 7.219 (4.499 – 11.581)      | < 0.0001                    |
|                      |                             | 7.630 (3.812 – 15.273)      | < 0.0001 |
| II with high LNR     | 9.423 (6.170 – 14.392)      | < 0.0001                    |
|                      |                             | 8.857 (4.941 – 15.877)      | < 0.0001 |
| III with low LNR     | 2.117 (0.292 – 15.344)      | 0.4580                      |
|                      |                             | 2.220 (0.282 – 17.453)      | 0.4480  |
| III with high LNR    | 10.646 (4.233 – 26.779)     | < 0.0001                    |
|                      |                             | 9.516 (3.202 – 28.281)      | < 0.0001 |
| IV with low LNR      | 18.018 (10.062 – 32.266)    | < 0.0001                    |
|                      |                             | 17.423 (7.681 – 39.522)     | < 0.0001 |
| IV with high LNR     | 15.309 (8.257 – 28.382)     | < 0.0001                    |
|                      |                             | 12.560 (5.337 – 29.556)     | < 0.0001 |
### Table 6. Univariate and multivariate analyses of baseline variables for recurrence-free survival with ATA risk stratification.

|                | Univariate |        | Multivariate |        |
|----------------|------------|--------|--------------|--------|
|                | HR (95% CI) | p value | HR (95% CI)  | p value |
| **2015 ATA risk category** |           |        |              |        |
| Low            | reference  |        | reference    |        |
| Intermediate   | 2.172 (1.152 – 4.097) | 0.0170 | 2.195 (1.159 – 4.157) | 0.0160 |
| High           | 6.610 (3.696 – 11.822) | < 0.0001 | 4.666 (2.502 – 8.704) | < 0.0001 |
| **2015 ATA risk category with LNR** |           |        |              |        |
| Low with low LNR | reference |        | reference    |        |
| Intermediate with low LNR | 0.700 (0.286 – 1.714) | 0.7000 | 0.750 (0.306 – 1.839) | 0.5300 |
| Intermediate with high LNR | 3.807 (1.992 – 7.275) | < 0.0001 | 3.811 (1.981 – 7.330) | < 0.0001 |
| High with low LNR  | 4.964 (2.692 – 9.154) | < 0.0001 | 3.793 (1.989 – 7.235) | < 0.0001 |
| High with high LNR | 7.892 (4.380 – 14.220) | < 0.0001 | 6.081 (3.230 – 11.447) | < 0.0001 |
Figure 1: Receiver operating characteristic (ROC) curve for lymph node ratio (LNR). Tumors with LNR of 0.15 predicted PTC recurrence with a sensitivity of 69%, specificity of 59%, and area under cover (AUC) of 0.668 ($p < 0.001$).