Original Article

Does preoperative neutrophil lymphocyte ratio predict risk of recurrence and occult central nodal metastasis in papillary thyroid carcinoma?

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Key words: papillary thyroid carcinoma, disease-free survival, central neck dissection, lymph node metastasis, radioiodine ablation

ABSTRACT

Background:

Preoperative neutrophil to lymphocyte ratio (NLR) might be prognostic in papillary thyroid carcinoma (PTC). Given the controversy of prophylactic central neck dissection (pCND) in clinically-nodal negative (cN0) PTC, our study evaluated whether preoperative NLR predicted disease-free survival (DFS) and occult central nodal metastasis (CNM) in cN0 PTC.

Methods:

One hundred and ninety-one patients who underwent pCND were analyzed. Complete blood counts with differential counts were taken before operation. NLR was calculated by dividing preoperative neutrophil count with lymphocyte count. Patients were categorized into NLR tertiles, namely the first (NLR<1.93) (n=63), second (NLR=1.93–2.79) (n=64) and third tertile (NLR>2.79) (n=64). Four other patient types namely, benign nodular goiter, clinically-nodal positive (cN1) PTC, poorly differentiated thyroid carcinoma and anaplastic thyroid carcinoma (ATC) were used as references.

Results:

Age at operation (p<0.001) and tumor size (p=0.037) significantly increased with higher NLR. First tertile had significantly more *TNM* Stage I tumors (p=0.010) and lowest *MACIS* score (p=0.002). Tumor size (HR=1.422,95%CI=1.119 – 1.809,p=0.004) and multicentricity (HR=2.545,95%CI=1.073 – 6.024,p=0.034) independently predicted DFS while old age (OR=1.026,95%CI=1.006 – 1.046, p=0.009), male (OR=2.882,95%CI=1.348 – 6.172,p=0.006) and large tumor (OR=1.567,95%CI=1.209 – 2.032,p=0.001) independently predicted occult

CNM. NLR was not significantly associated with DFS or occult CNM. ATC had significantly higher NLR than cN1 PTC (7.28 vs. 2.74,p<0.001).

Conclusions:

Although a higher NLR may imply a poorer tumor profile, it was not significantly associated with a worse DFS or higher risk of occult CNM in cN0 PTC. Perhaps, future research should focus on the prognostic value in other thyroid cancer types with a poorer prognosis.

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of differentiated thyroid carcinoma and its age-adjusted incidence has doubled in the last 25 years.[1] Despite its relatively good prognosis with a 10-year cancer-specific survival above 90%, locoregional recurrence (LRR) is common.[2] With recognition of the concept of step-wise progression of lymph node metastasis originating from the central (level VI) to the lateral compartment (levels II-V) and the fact that preoperative ultrasonography (USG) could only identify approximately half of the central nodal metastasis (CNM), a growing number of surgeons are advocating routine prophylactic central neck dissection (pCND) at the time of the total thyroidectomy (TT).[3-5] But since this appears to be at the expense of having higher surgical morbidities,[6] a more selective approach based on risk factors for CNM has been advocated.[7]

It has been recognized that systemic inflammation commonly occurs in the presence of many human cancers including thyroid carcinoma and the neutrophil to lymphocyte ratio (NLR) is one of the most reliable biomarkers for measuring the level of systemic inflammation.[8-10] NLR has been shown to be a convenient and inexpensive prognostic biomarker in many human cancers.[8-11] Potential mechanisms underlying the prognostic significance of NLR may be an association with lower immuno-competence, and/or lowering of the neutrophil count from a stimulating tumor microenvironment[8-11]. To our knowledge, only two studies have examined its significance in PTC.[12-13] Seretis et al. compared the NLR between those with an incidental papillary microcarcinoma and those with a benign goiter only and found that the former group had a significantly higher mean NLR than the latter group (3.0 vs. 1.9, $p<0.001$). The authors concluded that NLR could potentially be used as a biomarker for detecting incidental small PTC

in an apparently benign goiter.[12] Liu et al. studied the correlation between preoperative NLR and tumor characteristics and risk and found that a higher preoperative NLR was significantly associated with a larger-sized tumor and a greater risk of recurrence based on the American Thyroid Association (ATA) staging system.[13,14] As a result, NLR might be a promising serum biomarker for diagnosis and prognostication of PTC.

In view of these findings and the fact that one of the main controversies in PTC is deciding on whether to perform pCND or not at the time of TT in clinically-nodal negative (cN0) PTC, our study was aimed to evaluate the utility of preoperative NLR in determining disease-free survival (DFS) and in predicting occult CNM in cN0 PTC.

PATIENTS AND METHODS

Patients

From January 2004 – October 2012, 229 consecutive patients with cN0 PTC underwent a routine unilateral pCND at the time of TT and were retrospectively analyzed. All patients had no evidence of CNM on preoperative USG or at operation. To avoid possible confounders for NLR, patients with a condition known to affect the total and differential white cell count (WCC) such as hematologic disorder (n=9), other malignancy or cancer treatment within the last 12 months (n=20), acute myocardial infarction / coronary revascularization within 6 months (n=1), active infection or glucocorticoids use within 3 months (n=2), preoperative thyroid-stimulating hormone (TSH) outside normal range (i.e. <0.35 or >4.78mIU/L) (n=6) were excluded. After excluding these patients, 191 (83.4%) cN0 PTC patients were eligible for analysis. All patients had complete blood counts with automated differential counts taken one day before elective thyroidectomy. NLR was calculated by dividing the absolute neutrophil count with the absolute lymphocyte count. To evaluate the association between NLR and other tumor clinicopathologic features and outcomes, patients were categorized into 3 tertiles, namely the first tertile or group I (NLR<1.93) (n=63), the second tertile or group II (NLR=1.93 – 2.79) (n=64) and the third tertile or group III (NLR>2.79) (n=64).

To further appreciate the association between NLR and clinicopathologic features in other thyroid diseases, four other patient groups were analyzed. They comprised 192 patients with benign nodular goiter, 48 patients with clinically nodal (cN1) PTC, 20 patients with poorly differentiated thyroid carcinoma (PDTC) and 15 patients with anaplastic thyroid carcinoma (ATC) during the study period. They were selected based on the same exclusion criteria as above. Patients with follicular/hurthle cell adenoma or occult PTC were excluded. The WCC, neutrophil

and lymphocyte counts and NLR were compared between the benign goiter, cN0 PTC, cN1 PTC, PDTC and ATC groups.

Methods

All cell counts were done in our own institution's laboratory. All relevant clinical, laboratory, radiologic, and perioperative data were collected prospectively and follow-up data were regularly updated in a computerized database. The present study protocol was approved by the local institutional review board. Patient clinicopathological features and postoperative outcomes were compared between the three tertiles.

Management of PTC

Details of surgical treatment and follow-up protocol had been described previously.[15,16] A routine ipsilateral pCND was performed for all regardless of tumor size or extent.[15] The pCND consisted of the removal of all nodes and fibro-fatty tissue extending vertically from the hyoid bone to the thoracic inlet and laterally from the medial border of common carotid artery to the midline of the trachea. The ipsilateral recurrent laryngeal nerve was mobilized and skeletonized along its entire cervical course. An intraoperative nerve stimulator was used to confirm its functional integrity.[17] Parathyroid autotransplantation was readily performed. Stimulated thyroglobulin (sTg) was defined as a Tg level measured in the presence of TSH >30 mIU/L either by thyroxine withdrawal or recombinant TSH injections. The pre-ablation sTg level was taken approximately 2 months after surgery while the post-ablation level was taken approximately 9 months after surgery (6-7 months after RAI ablation). Tg autoantibodies were measured at the same time. The decision for RAI ablation was based on presence of ≥1 risk factors such as tumor size > 1.5cm, lymph node metastasis, age >45 years old, extrathyroidal

extension, macroscopic postoperative residual disease in the neck and distant metastasis. Three giga-Becquerels (GBq) or 80millicuries (mCi) I131 was the standard fixed ablative dose.

Follow-up protocol

All post-surgical patients were followed up within 4 weeks in a specialized combined oncology clinic. A follow-up visit was conducted at 3-month intervals in the first 2 years, 6-month in the subsequent 3 years and annually thereafter. Clinical examination, neck USG and non-stimulated Tg level were done during follow-up visits. LRRs were frequently diagnosed by USG, CT/ MRI or FDG-PET scan and confirmed by fine needle aspiration cytology.

Statistical analysis

Statistical analysis was performed by chi-square or Fisher's Exact test to compare categorical variables, and Mann-Whitney U or Kruskal-Wallis test was used to compare continuous variables between groups. For correlation between two continuous variables, the Pearson correlation test was performed. Continuous variables were expressed as mean±SD. Disease-free survival (DFS) was estimated using the Kaplan-Meier method and compared by the log-rank test. Linear regression was used to model the correlation between NLR and two or more continuous significant variables. Variables which were significant in the univariate analysis were entered into multivariate analysis. Cox regression or binary logistic regression analysis with a variable entrance criterion of 0.05 or less was conducted to identify independent factors. All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Our cohort was mostly females (79.1%) and ethnic Chinese (94.2%). The mean age at operation was 47.9 ± 15.8 years old. The mean (±SD) tumor size was 1.87 ± 1.36cm. The mean (±SD) total number of central lymph nodes (CLNs) and positives CLNs removed were 5.7 ± 1.0 and 2.6 ± 1.0, respectively. The mean (±SD) and median (range) NLR in our cohort were 2.68±1.84 and 2.29 (0.52 – 16.6), respectively. After a mean follow-up was 41.3 ± 26.5 months, all patients were still alive. There were 12 patients with recurrence and of these, 11 were confined locoregionally while 1 had locoregional and distant recurrences. The mean duration to first recurrence was 20.4 ± 15.3 months. The 5-year recurrence rate was 9.1%.

Table 1 shows a comparison of clinicopathological features, blood parameters, *TNM* tumor stages and *MACIS* score between the 3 tertiles. The mean age was significantly different (p<0.001) with the third tertile having the oldest age. There was a significant direct correlation between age and NLR (ρ= 0.281, p<0.001). Total WCC (p=0.002) and neutrophil count (p<0.001) were significantly higher with higher tertiles while lymphocyte count (p<0.001) was significantly lower with higher tertiles. Tumor size was also significantly increased with higher tertiles (p=0.037). However, there was no significant correlation between age and tumor size (ρ= -0.008, p=0.896). Tumor characteristics including tumor bilaterality, multifocality, capsular invasion, extrathyroidal extension, coexisting thyroiditis, presence of CNM, number of CLNs and positive CLNs were similar between the tertiles. Regarding *TNM* staging, the first tertile had more Stage I tumors than the second and third tertiles (71.4% vs. 53.1 and 48.4%, p=0.010). Although not significant, the first tertile tended to have less Stage III and IV tumors than the second and third tertiles (15.9% vs. 28.1% and 31.3% and 9.4% vs. 15.6% and 17.2%, respectively). The first tertile also had the lowest *MACIS* score when compared to the second and third tertiles (4.68 vs.

5.04 and 5.60, *p*=0.002). However, after adjusting for age in a regression analysis, neither *TNM* stages (*p*=0.335) nor *MACIS* (*p*=0.976) remained significantly correlated with NLR.

Figure 1 shows the cumulative DFS curves between the three tertiles.

Table 2 shows the Cox regression analysis for DFS. In the univariate analysis, tumor size (HR=1.403,95%CI=1.097 – 1.796,*p*=0.007), extrathyroidal extension (HR=2.290, 95%CI=1.026 – 5.113, *p*=0.043), multicentricity (HR=2.734,95%CI=1.170 – 6.390, *p*=0.020), lymphovascular permeation (HR=2.875,95%CI=1.287 – 6.426, *p*=0.010) and occult CNM (HR=3.083, 95%CI=1.302 – 7.978, *p*=0.002) were associated with a worse DFS. NLR did not significantly determine DFS. In the multivariate analysis, tumor size (HR=1.422; 95%CI=1.119 – 1.809, *p*=0.004) and multicentricity (HR=2.545,95%CI=1.073 – 6.024, *p*=0.034) independently predicted worse DFS.

Table 3a shows a comparison of patient clinicopathologic features and blood parameters between those with occult CNM (N1a group) and those without occult metastases (N0 group). The N1a group was significantly younger (45.2 years vs. 51.0 years, *p*=0.001), more male (28.2% vs. 15.9%, *p*=0.023), had larger tumor (2.42cm vs. 1.45cm, *p*=0.001) and more lymphovascular permeation (35.9% vs. 15.9%, *p*=0.004). Tumor multicentricity almost reached significance (*p*=0.083). Other blood parameters including NLR were not significant. Table 3b shows the multivariate analysis for occult CNM. Younger age (OR=1.026, 95%CI=1.006 – 1.046, *p*=0.009), male sex (OR=2.882, 95%CI=1.348 – 6.172, *p*=0.006) and larger tumor size (OR=1.567, 95%CI=1.209 – 2.032, *p*=0.001) were independent predictors of occult CNM.

NLR in benign nodular goiter, cN1 PTC, PDTC and ATC

Unlike cN0 PTC, age was not significantly associated with NLR (p=0.883) in benign nodular goiter. There were also no significant associations between NLR and clinicopathologic features in the benign nodular goiter, cN1 PTC, PDTC and ATC groups.

Table 4 compares age and blood parameters between benign nodular goiter, cN0 PTC, cN1 PTC, PDTC and ATC. There were no significant differences in NLR between benign goiter and cN0 PTC (p=0.492), between cN0 PTC and cN1 PTC (p=0.951) and between PDTC and ATC (p=0.299) but there was a significant difference between cN1 PTC and ATC (p<0.001).

DISCUSSION

Although using NLR as a biomarker for predicting prognosis has been well demonstrated in many non-thyroidal cancers, the evidence supporting its role as a prognostic biomarker in PTC remains relatively scarce.[8-10,12,13] Nevertheless, using NLR as a biomarker is attractive because it is relatively cheap and more importantly, readily available. To our knowledge, two studies have examined the significance of NLR in PTC and one of them has found that the group with the higher NLR had significantly larger sized tumors and greater ATA risk for recurrence.[12,13]

Similar to this previous study, our data found a higher NLR implied a poorer tumor risk profile. The third tertile had significantly older patients (54.1 vs. 42.0 years, $p<0.001$) and larger sized tumors (1.92cm vs. 1.72cm, $p=0.037$) than first tertile and both age and tumor size appeared independent as there was no significant correlation between the two ($p=0.896$). Interestingly though, a similar relationship between NLR and age was not observed in benign nodular goiter and ATC and so this direct correlation between age and NLR might only be present in PTC only. Consistent to these findings, our data also found that the the first NLR tertile had significantly more *TNM* stage I tumors (71.4% vs. 48.4%, $p=0.010$) and lower *MACIS* score (4.68 vs. 5.60, $p=0.002$) than the third tertile. However, it should be noted that when age had been adjusted for in the regression analysis, neither *TNM* nor *MACIS* remained significantly correlated with NLR. The exact explanation for the poorer tumor risk profile remains unclear but since a higher NLR was a result of increased neutrophil count relative to lymphocyte count, one possible explanation would be that activated neutrophils might directly or indirectly stimulate tumor growth as suggested in previous studies.[18] Although the relationship between NLR and

age was not reported in the two previous studies on PTC and in our small cohort of ATC,[12,13] this was observed in other non-thyroidal cancers.[9-10]

Given the controversy of pCND and the significant correlation between NLR and age, tumor size, *TNM* stage I and *MACIS* score, it was further analyzed to determine whether it was associated with DFS and occult CNM in cN0 PTC. In the univariate analysis for DFS, even though the hazard ratio was greater than one, NLR did not reach significance (HR=1.127, 95%CI=0.932 – 1.363, p=0.224). In the multivariate analysis, after adjusting for extrathyroidal extension, lymphovascular permeation and N1a, larger tumor size (HR=1.422, 95%CI=1.119 – 1.809, p=0.004) and multicentricity (HR=2.545, 95%CI=1.073 – 6.024, p=0.034) turned out to be independent predictors for worse DFS. This was consistent to our previous analysis which found that tumor size was a risk factor for having detectable post-ablative stimulated Tg (a surrogate for persistent / recurrent disease) in cN0 PTC.[19] A recent study has also reported similar findings with tumor size (OR=1.93) and extrathyroidal extension (OR=12.47) as risk factors for LRR in cN0 PTC.[19] Interestingly, this study also found adding pCND reduced LRR (OR=0.21, 95%CI=0.11 – 0.41, p<0.001).[20]

In the univariate analysis for occult CNM, although the mean NLR appeared greater in the N1a group than N0 group, it was not significantly different (2.70 vs 1.41, p=0.275) and so NLR was not entered into the multivariate analysis. Consistent with other previous studies, our data showed that younger age (OR=1.026, 95%CI=1.006 – 1.046, p=0.009), male sex (OR=2.882, 95%CI=1.348 – 6.172, p=0.006) and larger tumor size (OR=1.567, 95%CI=1.209 – 2.032, p=0.001) were independent predictors for occult CNM in cN0 PTC.[7,21-26] However, unlike previous studies,[21,22,26] lymphovascular permeation turned out to be significant only in the

univariate and not in the multivariate analysis (OD=1.946, 95%CI=0.919 – 4.122, *p*=0.082). Other significant predictors for occult CNM included extrathyroidal extension and multicentricity but they were not found to be significant in the present analysis.[7,21-23,25-27] Although the presence of *BRAF* mutation in the primary tumor has been found to be a possible predictor for occult CNM, this has not been consistently shown and was not assessed here.[26,28]

Therefore, although a higher NLR may imply a poorer tumor profile, it was not significantly enough to predict a worse DFS or higher risk of occult CNM in cN0 PTC. One possible reason might be because the prognosis of cN0 PTC is generally very good and so its NLR is expected to be within the low and narrow range (mean±SD was 2.70±1.91). In fact, NLR were not significantly different between benign nodular goiter and cN0 PTC, between cN0 PTC and cN1 PTC and between PDTC and ATC (see Table 4). There was only a significant difference in NLR between cN0 PTC and ATC ($p<0.001$). These data implied that NLR might be an indicator for histological differentiation and prognosis but not a strong enough indicator for differentiating between cN0 and cN1 PTC or between PDTC and ATC.

However, despite these findings, our data should be interpreted cautiously as this was a relatively moderate-sized study and that tended to limit the power of the study to identify smaller effects. Also since this study was retrospective, it was prone to selection biases.

Conclusion

Although a higher preoperative NLR was significantly associated with older age at operation, larger primary tumor size, more advanced *TNM* stages and higher *MACIS* score, it did not predict a worse DFS or risk of occult CNM in patients with cN0 PTC. Perhaps, a larger-scale

prospective study should be conducted to further evaluate the prognostic significance of preoperative NLR in other thyroid cancer types with a significantly worse prognosis than PTC. Clinicopathologic factors remained more significant predictors of DFS and occult CNM.

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Table 1. A comparison of patient clinicopathological features, blood parameters, *TNM* tumor stages and MACIS score between those with a neutrophil lymphocyte ratio (NLR) < 1.93 (First tertile), NLR = 1.93 – 2.79 (Second tertile) and NLR > 2.79 (Third tertile).

	First tertile (NLR<1.93) (n=63)	**Second tertile (NLR=1.93 – 2.79) (n=64)**	**Third tertile (NLR>2.79) (n=64)**	***p*-value**
Age at operation (years)	42.03 ± 16.04	50.42 ± 13.47	54.13 ± 15.06	**<0.001**
Sex - Male - Female	 9 (14.3) 54 (85.7)	 14 (21.9) 50 (78.1)	 17 (26.6) 47 (73.4)	0.230
Presented as a palpable neck swelling	17 (27.0)	25 (39.1)	26 (40.6)	0.214
Serum TSH (mIU/L)	1.55 ± 1.10	1.40 ± 0.99	1.34 ± 0.99	0.685
Hemoglobin (g/dL)	12.82 ± 1.36	13.02 ± 1.45	12.68 ± 1.65	0.390
Platelet count (10^9/L)	258.62 ± 68.51	253.69 ± 64.27	241.98 ± 75.78	0.274
Total white cell count (10^9/L)	5.64 ± 1.49	6.36 ± 1.52	6.72 ± 1.94	**0.002**
Neutrophil count (10^9/L)	2.95 ± 0.91	4.00 ± 1.01	4.92 ± 1.60	**<0.001**
Lymphocyte count (10^9/L)	2.13 ± 0.66	1.76 ± 0.43	1.24 ± 0.39	**<0.001**

Neutrophil lymphocyte ratio	1.41 ± 0.35	2.28 ± 0.25	4.39 ± 1.9	**<0.001**
Tumor characteristics				
- Tumor size (cm)	1.46 ± 1.47	1.81 ± 1.10	2.13 ± 1.31	**0.037**
- Tumor bilaterality	17 (27.0)	18 (28.1)	15 (23.4)	0.820
- Multifocality	25 (39.7)	24 (37.5)	23 (35.9)	0.644
- Extra-thyroidal extension	19 (30.2)	23 (35.9)	18 (28.1)	0.566
- LV permeation	10 (15.9)	15 (23.4)	11 (17.2)	0.309
- Coexisting thyroiditis	13 (20.6)	10 (15.6)	14 (21.9)	0.639
- Occult CNM (pN1a)	23 (36.5)	27 (42.2)	28 (43.8)	0.215
Follicular-variant of PTC	7 (11.1)	5 (7.8)	9 (14.1)	0.377
Number of central lymph nodes retrieved	5.5 ± 1.0	5.7 ± 1.0	6.3 ± 1.0	0.969
Number of metastatic central lymph nodes excised	2.6 ± 1.0	2.6 ± 1.0	2.6 ± 1.0	0.192
Stage of PTC by *TNM*				
- Stage I	45 (71.4)	34 (53.1)	31 (48.4)	**0.010**
- Stage II	2 (3.2)	2 (3.1)	2 (3.1)	1.000

- Stage III - Stage IV	10 (15.9) 6 (9.4)	18 (28.1) 10 (15.6)	20 (31.3) 11 (17.2)	0.098 0.210
Radioiodine ablation	47 (74.6)	48 (75.0)	49 (76.6)	0.952
Pre-ablation sTg level (mIU/L)	1.5 ± 0.9	1.2 ± 0.9	2.2 ± 0.9	0.222
Post-ablation sTg level (mIU/L)	0.2 ± 0.1	0.4 ± 0.2	0.5 ± 0.2	0.456
MACIS score	4.68 ± 1.39	5.04 ± 1.10	5.60 ± 1.20	**0.002**

Continuous variables are expressed as median (range); categorical variables are expressed as number (percentage)

Abbreviations: PTC = papillary thyroid carcinoma; LV= lymphovascular; CNM = central nodal metastasis; *TNM* = 7th edition Tumor, Node and Metastasis staging system; *MACIS* = Metastases, Age, Completeness of surgery, Invasion and Size; sTg = stimulated thyroglobulin

Table 2. Cox regression analysis of disease-free survival in 191 clinically-nodal negative (cN0) papillary thyroid carcinoma

	Univariate analysis			Multivariate analysis		
Variable	**Hazard ratio**	**95% CI**	***p*-value**	**Hazard ratio**	**95% CI**	***p*-value**
Age	0.984	0.959 – 1.010	0.229			
Female sex	0.536	0.229 – 1.254	0.150			
TSH	0.656	0.355 – 1.212	0.178			
Tumor size	1.403	1.097 – 1.796	**0.007**	1.422	1.119 – 1.809	**0.004**
ETE	2.290	1.026 – 5.113	**0.043**	0.604	0.268 – 1.363	0.225
Multicentricity	2.734	1.170 – 6.390	**0.020**	2.545	1.073 – 6.024	**0.034**
LV permeation	2.875	1.287 – 6.426	**0.010**	1.869	0.811 – 1.869	0.142
N1a	3.016	1.122 – 8.106	**0.029**	2.227	0.816 – 6.098	0.118
Tumor bilaterality	1.034	0.410 – 2.605	0.944			
White cell count	1.190	0.940 – 1.505	0.148			
NLR	1.127	0.932 – 1.363	0.219			
Neutrophil count	1.192	0.906 – 1.570	0.210			

Lymphocyte count	1.336	0.601 – 2.970	0.477			
RAI ablation	1.492	0.343 – 6.492	0.594			

Abbreviations: TSH = thyroid stimulating hormone; ETE = extrathyroidal extension; LV = lymphovascular; N1a = occult central lymph node metastases; NLR = neutrophil to lymphocyte ratio; CI = confidence interval; RAI = radioiodine

Bold letters signify statistical significance ($p<0.05$)

Table 3a. A comparison of patient clinicopathologic features and blood parameters between those with occult central nodal metastases (N1a) and those without occult central nodal metastases (N0)

	N1a group (n=78)	**N0 group (n=113)**	***p*-value**
Age at operation (years)	45.21 ± 17.15	51.04 ± 13.32	**0.001**
Sex (Male : Female)	22 : 56	18 : 95	**0.023**
Serum TSH (mIU/L)	1.55 ± 1.03	1.41 ± 0.96	0.965
Hemoglobin (g/dL)	12.85 ± 1.58	12.85 ± 1.39	0.175
Platelet count (10^9/L)	247.96 ± 68.62	254.15 ± 70.51	0.712
Total white cell count (10^9/L)	6.17 ± 1.81	6.35 ± 1.62	0.233
Neutrophil count (10^9/L)	3.85 ± 1.56	4.10 ± 1.31	0.183
Lymphocyte count (10^9/L)	1.74 ± 0.69	1.68 ± 0.54	0.781
Neutrophil lymphocyte ratio	2.70 ± 1.42	1.41 ± 0.96	0.275
Tumor characteristics			
- Tumor size (cm)	2.42 ± 1.45	1.45 ± 1.11	**0.001**
- Tumor bilaterality	22 (28.2)	28 (24.8)	0.627
- Multifocality	27 (34.6)	45 (39.8)	0.352

- Extra-thyroidal extension	30 (38.5)	30 (26.5)	0.083
- LV permeation	28 (35.9)	18 (15.9)	**0.004**

Table 3b. A multivariable analysis of clinicopathological risk factors for occult central lymph node metastases (N1a)

Covariates	**ß-coefficient**	**Odds ratio (95% confidence interval)**	***p*-value**
Age at operation	-0.026	1.026 (1.006 – 1.046)	**0.009**
Male sex	1.065	2.882 (1.348 - 6.172)	**0.006**
Tumor size	0.444	1.567 (1.209 – 2.032)	**0.001**
LV permeation	1.058	1.946 (0.919 – 4.122)	0.082

Abbreviations: TSH = thyroid stimulating hormone; LV = lymphovascular

Table 4 shows a comparison of age and blood parameters between benign nodular goiter, clinically-nodal negative (cN0) and positive (cN1) papillary thyroid carcinoma (PTC), poorly differentiated thyroid carcinoma (PDTC) and anaplastic thyroid carcinoma (ATC)

	Benign goiter (n=192)	**cN0 PTC (n=191)**	**cN1 PTC (n=58)**	**PDTC (n=13)**	**ATC (n=15)**	**p-value***	**p-value+**	**p-value#**	**p-value^**
Age at operation (yrs)	49.52 ± 14.17	47.90 ± 15.80	50.47 ± 8.7	72.0 ± 18.47	76.73 ± 8.75	0.589	0.441	**<0.001**	**0.818**
Total white cell count (10^9/L)	6.33 ± 1.83	6.38 ± 1.90	6.39 ± 1.95	6.43 ± 4.16	10.34 ± 4.23	0.930	0.866	**<0.001**	**0.004**
Neutrophil count (10^9/L)	4.10 ± 1.64	4.02 ± 1.51	3.87 ± 1.18	4.73 ± 4.21	8.06 ± 4.23	0.868	0.674	**<0.001**	**0.006**
Lymphocyte count (10^9/L)	1.66 ± 0.55	1.73 ± 0.61	1.74 ± 0.76	1.07 ± 0.52	1.36 ± 0.61	0.336	0.532	0.123	0.181
Neutrophil lymphocyte ratio	2.80 ± 1.77	2.68 ± 1.84	2.74 ± 2.32	6.36 ± 6.68	7.28 ± 4.64	0.492	0.951	**<0.001**	0.299

*between benign nodular goiter and cN0 PTC

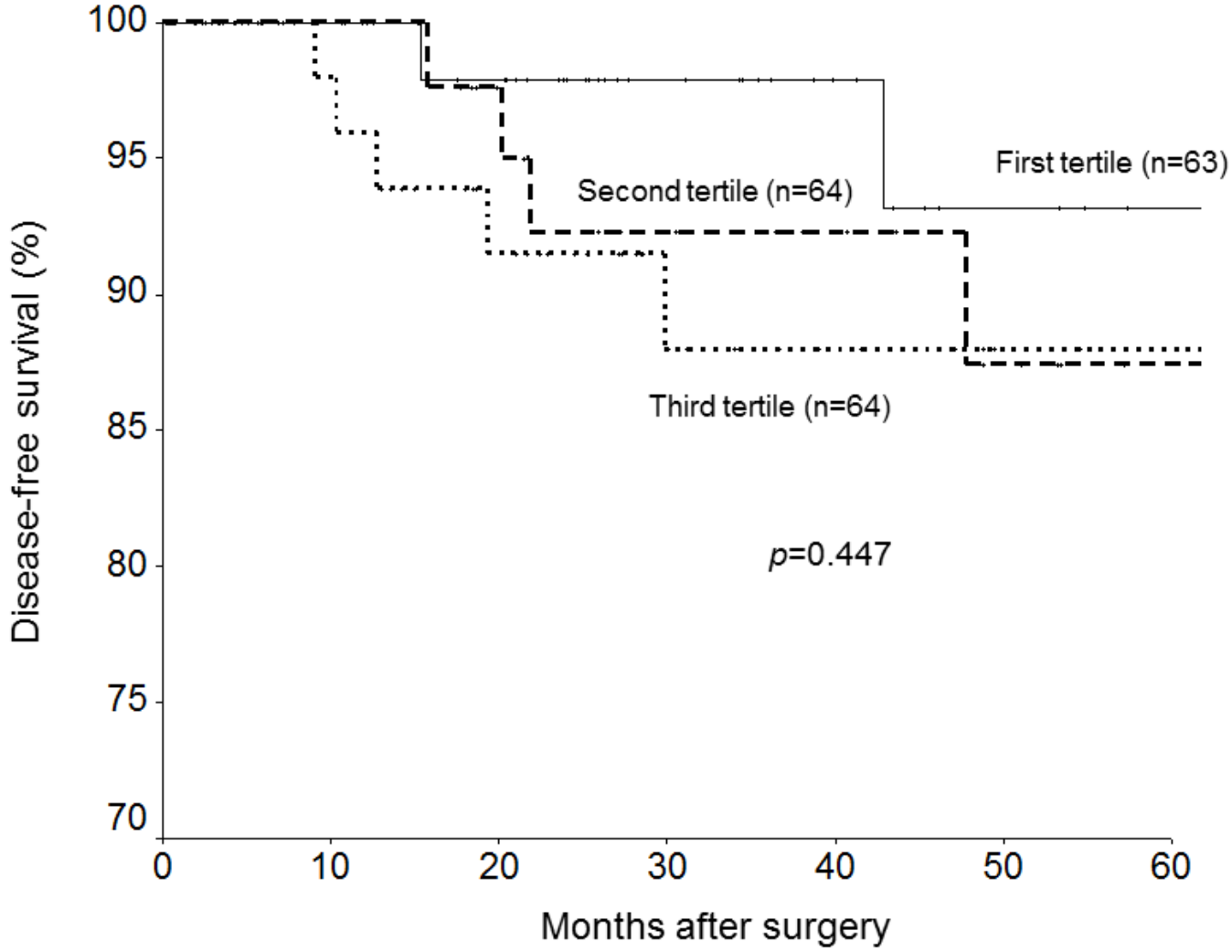
+between cN0 PTC and cN1 PTC

#between cN1 PTC and ATC

^between PDTC and ATC

LEGENDS

Figure 1. The cumulative disease-free survival curves of clinically nodal negative papillary thyroid carcinoma with a preoperative neutrophil to lymphocyte ratio (NLR) < 1.93 (n=63, first tertile), NLR = 1.93 – 2.79 (n=64, second tertile) and NLR > 2.79 (n=64, third tertile)


100
95
90
85
80
75
70
Disease-free survival (%)
0
10
20
30
40
50
60
Months after surgery
First tertile (n=63)
Second tertile (n=64)
Third tertile (n=64)
p=0.447