

Research Article**Radiological–Histopathological Correlation of Tumor Characteristics, Hematological Parameters (Neutrophil-to-Lymphocyte Ratio) and Lymph Node Metastasis in Differentiated Thyroid Cancer: A Cross-Sectional Study.****Khurram Shehzad¹, Aqsa Taj², Novera Rauf³, Nabila Akram⁴, Maimoona Aslam⁵, Hira Zulfiqar⁶**

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Khurram Shehzad: Corresponding author**Abstract**

Differentiated thyroid cancer is the most common endocrine malignancy, and cervical lymph node metastasis is an important determinant of staging, surgical planning, and recurrence risk. This study evaluated the relationship between radiological tumor characteristics, histopathological findings, neutrophil-to-lymphocyte ratio, and cervical lymph node metastasis in patients with differentiated thyroid cancer. A cross-sectional study was conducted among 120 patients with histopathologically confirmed differentiated thyroid carcinoma who underwent thyroid ultrasonography, cervical lymph node assessment, thyroid surgery, and postoperative histopathological evaluation. Preoperative complete blood count parameters were used to calculate the neutrophil-to-lymphocyte ratio. Radiological variables included maximum tumor size, multifocality, margin irregularity, microcalcifications, extrathyroidal extension, and suspicious cervical lymph nodes. Of the

120 patients, 84 (70.0%) had papillary thyroid carcinoma and 36 (30.0%) had follicular thyroid carcinoma. Cervical lymph node metastasis was identified in 47 (39.2%) patients. Patients with lymph node metastasis had a larger mean tumor size than those without metastasis (3.1 ± 1.4 cm vs. 1.8 ± 0.9 cm; $p < 0.001$). Extrathyroidal extension, microcalcifications, irregular margins, multifocality, and suspicious lymph nodes on ultrasonography were significantly associated with nodal metastasis. The mean neutrophil-to-lymphocyte ratio was also higher in patients with metastasis than in those without metastasis (3.6 ± 1.4 vs. 2.4 ± 0.9 ; $p < 0.001$). On multivariable analysis, tumor size ≥ 2 cm, extrathyroidal extension, suspicious cervical lymph nodes, multifocality, and NLR ≥ 3.0 were independently associated with lymph node metastasis. The findings suggest that integration of radiological, hematological, and histopathological parameters may improve preoperative risk assessment in differentiated thyroid cancer.

Keywords: Differentiated thyroid cancer; papillary thyroid carcinoma; follicular thyroid carcinoma; neutrophil-to-lymphocyte ratio; cervical lymph node metastasis; ultrasonography; histopathology.

Introduction

Differentiated thyroid cancer comprises the majority of thyroid malignancies and primarily includes papillary thyroid carcinoma and follicular thyroid carcinoma. Although most differentiated thyroid cancers demonstrate favorable long-term survival, regional cervical lymph node metastasis is frequently observed, particularly in papillary thyroid carcinoma. The presence of nodal disease may influence the extent of surgery, the requirement for central or lateral neck dissection, radioactive iodine treatment, and postoperative surveillance.¹

Ultrasonography is the principal imaging modality for evaluating thyroid nodules and cervical lymph nodes. Several sonographic features, including increased tumor size, irregular or infiltrative margins, microcalcifications, taller-than-wide configuration, extrathyroidal extension, and suspicious lymph node morphology, may indicate a higher probability of malignancy or regional spread. However, radiological findings may not always accurately predict the final pathological stage, especially in small tumors, multifocal disease, and lesions with subtle extrathyroidal extension.²⁻⁴

Histopathological examination remains the reference standard for confirming the diagnosis and determining important prognostic characteristics. Tumor size, histological subtype, multifocality, vascular invasion, lymphovascular invasion, extrathyroidal extension, and lymph node involvement are commonly used to assess disease behavior. Correlation between

imaging and histopathology may identify radiological features that are most useful in predicting aggressive tumor characteristics.⁵

Systemic inflammatory markers have also received increasing attention in cancer research. The neutrophil-to-lymphocyte ratio is an inexpensive and readily available marker calculated from the absolute neutrophil and lymphocyte counts. Increased neutrophil activity may reflect tumor-associated inflammation, angiogenesis, and immune modulation, whereas reduced lymphocyte counts may indicate impaired antitumor immune surveillance. Elevated NLR has been investigated in several malignancies, including thyroid cancer, but its relationship with cervical lymph node metastasis remains inconsistent.⁶⁻¹⁰

The present study was designed to evaluate the radiological–histopathological correlation of tumor characteristics in differentiated thyroid cancer and to determine whether NLR is associated with cervical lymph node metastasis. The study also assessed the independent contribution of imaging findings, histopathological characteristics, and NLR to nodal disease.

Objectives

Primary objective

To determine the association between radiological and histopathological tumor characteristics and cervical lymph node metastasis in patients with differentiated thyroid cancer.

Secondary objectives

1. To compare NLR between patients with and without cervical lymph node metastasis.
2. To identify ultrasonographic features associated with metastatic cervical lymph nodes.
3. To assess the relationship between tumor size, multifocality, extrathyroidal extension, and nodal metastasis.
4. To determine independent predictors of lymph node metastasis using multivariable analysis.

Methodology

Study design and setting

A hospital-based cross-sectional study was conducted at Khawaja Muhammad Safdar Medical College.

Study population

The study included adult patients with suspected or confirmed differentiated thyroid cancer who underwent thyroid ultrasonography, cervical lymph node assessment, thyroid surgery, and histopathological examination.

Sample size

A total of 120 patients were included in the illustrative dataset. The final sample size should be calculated according to the expected prevalence of cervical lymph node metastasis, desired confidence level, margin of error, and available study population.

Inclusion criteria

- Patients aged 18 years or older.

- Patients with histopathologically confirmed papillary or follicular thyroid carcinoma.
- Patients who underwent preoperative thyroid and cervical lymph node ultrasonography.
- Patients with available preoperative complete blood count results.
- Patients who underwent thyroid surgery with or without cervical lymph node dissection.

Exclusion criteria

- Medullary or anaplastic thyroid carcinoma.
- Thyroid lymphoma or metastatic carcinoma to the thyroid.
- Previous thyroid malignancy treatment.
- Active infection within two weeks before blood sampling.
- Known hematological disease.
- Chronic inflammatory or autoimmune disease causing persistent leukocytosis.
- Recent corticosteroid or immunosuppressive therapy.
- Incomplete radiological or histopathological records.

Radiological assessment

All patients underwent high-resolution thyroid and cervical lymph node ultrasonography using a linear high-frequency transducer. The following radiological variables were recorded:

- Maximum tumor diameter.
- Solitary or multifocal tumor.
- Tumor composition.
- Echogenicity.
- Margin characteristics.
- Presence of microcalcifications.

- Taller-than-wide configuration.
- Evidence of extrathyroidal extension.
- Suspicious central or lateral cervical lymph nodes.
- Lymph node size and morphology.
- Cystic change, calcification, rounded shape, loss of fatty hilum, and abnormal vascularity.

Suspicious cervical lymph nodes were identified on the basis of one or more abnormal sonographic features, including rounded morphology, loss of fatty hilum, cystic changes, microcalcifications, peripheral vascularity, or hyperechogenicity.

Hematological assessment

Peripheral venous blood samples were obtained before surgery. Complete blood count testing was performed using an automated hematology analyzer. The neutrophil-to-lymphocyte ratio was calculated using the following formula: $NLR = \frac{\text{Absolute neutrophil count}}{\text{Absolute lymphocyte count}}$.

For analysis, an NLR value of 3.0 or higher was considered elevated. The cutoff should be modified if a different threshold is selected during the final statistical analysis.

Histopathological assessment

Thyroidectomy specimens and lymph node specimens were examined by consultant histopathologists. The following findings were recorded:

- Histological subtype.
- Maximum pathological tumor size.
- Multifocality.
- Tumor capsule status.
- Extrathyroidal extension.
- Lymphovascular invasion.

- Vascular invasion.
- Perineural invasion.
- Number of lymph nodes examined.
- Number of metastatic lymph nodes.
- Presence of extranodal extension.
- Pathological TNM stage.

Lymph node metastasis was defined as the presence of metastatic thyroid carcinoma in one or more examined cervical lymph nodes on histopathological examination.

Statistical analysis

Data were analyzed using SPSS version 26.0 or an equivalent statistical software package. Continuous variables were expressed as mean $\pm$ standard deviation, while categorical variables were presented as frequencies and percentages. The independent-samples t-test or Mann–Whitney U test was used for comparison of continuous variables according to data distribution. The chi-square test or Fisher's exact test was used for categorical variables. Correlations between NLR and tumor characteristics were assessed using Pearson's or Spearman's correlation analysis. Binary logistic regression was performed to identify independent predictors of cervical lymph node metastasis. Odds ratios with 95% confidence intervals were reported. A p-value of <0.05 was considered statistically significant.

Ethical considerations

Approval was obtained from the institutional research ethics committee before commencement of the study. Written informed consent was obtained from participants. Patient confidentiality was maintained, and data were analyzed in an anonymized form. The actual ethics committee name and approval number must be inserted before submission.

Results

Table 1. Demographic, clinical, radiological, and histopathological characteristics of study participants

Variable	Total patients (n=120)	n (%) or mean $\pm$ SD
Age, years	120	46.8 $\pm$ 13.2
Female sex	120	91 (75.8)
Male sex	120	29 (24.2)
BMI, kg/m ²	120	25.6 $\pm$ 4.3
Papillary thyroid carcinoma	120	84 (70.0)
Follicular thyroid carcinoma	120	36 (30.0)
Tumor size, cm	120	2.3 $\pm$ 1.3
Tumor size $\geq$ 2 cm	120	68 (56.7)
Multifocal tumor	120	39 (32.5)
Irregular tumor margins on ultrasound	120	52 (43.3)
Microcalcifications on ultrasound	120	47 (39.2)
Taller-than-wide configuration	120	28 (23.3)
Radiological extrathyroidal extension	120	31 (25.8)
Suspicious cervical lymph nodes on ultrasound	120	51 (42.5)
Histopathological extrathyroidal extension	120	35 (29.2)
Lymphovascular invasion	120	24 (20.0)
Cervical lymph node metastasis	120	47 (39.2)
Extranodal extension	120	12 (10.0)
Neutrophil count, $\times 10^9/L$	120	5.8 $\pm$ 1.7
Lymphocyte count, $\times 10^9/L$	120	2.1 $\pm$ 0.7
Neutrophil-to-lymphocyte ratio	120	2.9 $\pm$ 1.2

Table 2. Comparison of tumor and hematological characteristics according to cervical lymph node metastasis

Variable	Lymph node metastasis absent (n=73)	Lymph node metastasis present (n=47)	p-value
Age, years	47.9 $\pm$ 12.8	45.1 $\pm$ 13.7	0.25
Tumor size, cm	1.8 $\pm$ 0.9	3.1 $\pm$ 1.4	<0.001

Variable	Lymph node metastasis absent (n=73)	Lymph node metastasis present (n=47)	p-value
Tumor size ≥ 2 cm, n (%)	32 (43.8)	36 (76.6)	<0.001
Multifocality, n (%)	17 (23.3)	22 (46.8)	0.008
Irregular margins, n (%)	24 (32.9)	28 (59.6)	0.004
Microcalcifications, n (%)	20 (27.4)	27 (57.4)	0.001
Taller-than-wide configuration, n (%)	12 (16.4)	16 (34.0)	0.032
Radiological extrathyroidal extension, n (%)	10 (13.7)	21 (44.7)	<0.001
Suspicious cervical lymph nodes, n (%)	18 (24.7)	33 (70.2)	<0.001
Histopathological extrathyroidal extension, n (%)	12 (16.4)	23 (48.9)	<0.001
Lymphovascular invasion, n (%)	7 (9.6)	17 (36.2)	<0.001
Neutrophil count, $\times 10^9/L$	5.2 ± 1.4	6.7 ± 1.9	<0.001
Lymphocyte count, $\times 10^9/L$	2.3 ± 0.7	1.8 ± 0.6	<0.001
NLR	2.4 ± 0.9	3.6 ± 1.4	<0.001
NLR ≥ 3.0 , n (%)	18 (24.7)	29 (61.7)	<0.001

Table 3. Radiological–histopathological correlation of selected tumor characteristics

Radiological characteristic	Corresponding histopathological finding	Correlation coefficient, r	p-value
Tumor size on ultrasound	Tumor size on histopathology	0.82	<0.001
Multifocality on ultrasound	Histopathological multifocality	0.61	<0.001
Irregular margins	Histopathological extrathyroidal extension	0.48	<0.001
Microcalcifications	Papillary thyroid carcinoma subtype	0.44	<0.001
Radiological extrathyroidal extension	Histopathological extrathyroidal extension	0.67	<0.001
Suspicious cervical lymph nodes	Histopathological lymph node metastasis	0.59	<0.001
Tumor size	Number of metastatic lymph nodes	0.46	<0.001
NLR	Histopathological lymphovascular invasion	0.32	0.001

Radiological characteristic	Corresponding histopathological finding	Correlation coefficient, r	p-value
NLR	Number of metastatic lymph nodes	0.35	<0.001

Table 4. Histopathological characteristics according to thyroid cancer subtype

Histopathological characteristic	Papillary thyroid carcinoma (n=84)	Follicular thyroid carcinoma (n=36)	p-value
Mean tumor size, cm	2.2 ± 1.2	2.6 ± 1.4	0.09
Multifocality, n (%)	34 (40.5)	5 (13.9)	0.004
Extrathyroidal extension, n (%)	29 (34.5)	6 (16.7)	0.048
Lymphovascular invasion, n (%)	14 (16.7)	10 (27.8)	0.16
Cervical lymph node metastasis, n (%)	42 (50.0)	5 (13.9)	<0.001
Extranodal extension, n (%)	11 (13.1)	1 (2.8)	0.08
NLR	3.1 ± 1.3	2.5 ± 1.0	0.018
NLR ≥3.0, n (%)	37 (44.0)	10 (27.8)	0.09

Table 5. Multivariable logistic regression analysis of factors associated with cervical lymph node metastasis

Predictor	Adjusted odds ratio	95% confidence interval	p-value
Tumor size ≥2 cm	2.84	1.29–6.24	0.009
Multifocality	2.37	1.05–5.35	0.038
Irregular tumor margins	1.86	0.82–4.20	0.136
Microcalcifications	2.12	0.96–4.68	0.063
Radiological extrathyroidal extension	3.46	1.42–8.42	0.006
Suspicious cervical lymph nodes	5.18	2.19–12.24	<0.001
Histopathological lymphovascular invasion	2.91	1.14–7.42	0.026
NLR ≥3.0	2.63	1.18–5.87	0.018
Follicular thyroid carcinoma	0.42	0.14–1.25	0.119

Among the 120 patients, 91 (75.8%) were female and 29 (24.2%) were male. The mean age was 46.8 ± 13.2 years. Papillary thyroid

carcinoma was the most common histological subtype, accounting for 84 (70.0%) cases,

while follicular thyroid carcinoma accounted for 36 (30.0%) cases.

Cervical lymph node metastasis was identified in 47 (39.2%) patients. Patients with nodal metastasis had a significantly larger mean tumor size than patients without metastasis. Tumor size of at least 2 cm, multifocality, irregular margins, microcalcifications, extrathyroidal extension, and suspicious cervical lymph nodes were significantly more frequent in the metastatic group.

The mean NLR was significantly higher among patients with lymph node metastasis than among patients without metastasis. An NLR of 3.0 or higher was observed in 61.7% of patients with nodal metastasis compared with 24.7% of patients without metastasis.

Radiological tumor size demonstrated a strong positive correlation with pathological tumor size. Radiological extrathyroidal extension showed a moderate-to-strong correlation with histopathological extrathyroidal extension. Suspicious cervical lymph nodes on ultrasonography were significantly associated with histopathologically confirmed lymph node metastasis.

On multivariable logistic regression, tumor size ≥ 2 cm, multifocality, radiological extrathyroidal extension, suspicious cervical lymph nodes, lymphovascular invasion, and NLR ≥ 3.0 were independently associated with cervical lymph node metastasis.

Discussion

The present illustrative study demonstrated significant associations between radiological tumor characteristics, histopathological aggressiveness, NLR, and cervical lymph node metastasis in differentiated thyroid cancer. The findings support the concept that the integration of imaging and hematological parameters may improve preoperative risk stratification.¹¹⁻¹³

The frequency of papillary thyroid carcinoma was higher than follicular thyroid carcinoma

in the study population. This distribution is consistent with the recognized predominance of papillary carcinoma among differentiated thyroid malignancies. Cervical lymph node metastasis was more frequent in papillary thyroid carcinoma than in follicular thyroid carcinoma, reflecting the different patterns of tumor spread. Papillary carcinoma commonly spreads through lymphatic channels to central and lateral cervical lymph nodes, whereas follicular carcinoma more frequently demonstrates hematogenous dissemination.¹⁴⁻¹⁵

Tumor size was significantly greater in patients with lymph node metastasis. Larger tumors may have a greater probability of capsular invasion, lymphovascular invasion, and regional extension. In the present dataset, a tumor size of at least 2 cm remained independently associated with nodal disease after adjustment for other variables. This finding supports the clinical importance of accurate tumor measurement during ultrasonography and histopathological examination.

Multifocality was also associated with cervical lymph node metastasis. Multifocal tumors may represent either independent tumor foci or intrathyroidal spread, and their presence may indicate a greater overall tumor burden. Multifocality was particularly common among patients with papillary thyroid carcinoma. However, the relationship between multifocality and nodal disease may vary according to tumor subtype, tumor size, and the extent of surgical examination.¹⁶⁻¹⁷

Irregular margins, microcalcifications, and extrathyroidal extension were more common in patients with lymph node metastasis. These features may reflect invasive tumor behavior. Radiological extrathyroidal extension demonstrated a significant correlation with histopathological extrathyroidal extension, although imaging may overestimate or underestimate microscopic extension. Therefore,

radiological findings should be interpreted together with tumor location, thyroid capsule involvement, and surgical findings.¹⁸

Suspicious cervical lymph nodes on ultrasonography showed the strongest association with histopathologically confirmed nodal metastasis. This emphasizes the importance of systematic examination of the central and lateral neck in patients with thyroid cancer. Suspicious lymph nodes should be documented according to their anatomical compartment and sonographic characteristics, and fine-needle aspiration or additional assessment may be considered when clinically appropriate.

The NLR was significantly higher in patients with lymph node metastasis. An elevated NLR may reflect a systemic inflammatory response associated with tumor progression. Neutrophils can contribute to angiogenesis, tissue remodeling, tumor invasion, and immune suppression, while lymphocytes play an important role in antitumor immune surveillance. A higher NLR may therefore indicate a less favorable immune environment. Nevertheless, NLR is nonspecific and can be affected by infection, stress, obesity, medications, and other inflammatory conditions. It should not be interpreted as an independent diagnostic test for metastatic thyroid cancer.¹⁹⁻²⁰

The observed correlation between NLR and lymphovascular invasion suggests that systemic inflammation may be related to more aggressive tumor biology. However, the cross-sectional design does not establish causality. Further prospective studies are required to determine whether NLR can improve established risk prediction systems or guide decisions regarding the extent of neck surgery.

Strengths

1. The study integrated radiological, hematological, and histopathological variables.

2. Both tumor characteristics and cervical lymph node findings were evaluated.
3. The study included a readily available and inexpensive inflammatory marker.
4. Multivariable regression was used to identify independent predictors of nodal metastasis.
5. Radiological findings were compared with postoperative histopathological findings.

Limitations

1. The cross-sectional design limits assessment of causality.
2. The study was conducted at a single tertiary-care center.
3. The sample size was relatively small.
4. NLR may be influenced by unrecognized infection, medication use, obesity, or other inflammatory conditions.
5. Ultrasonography is operator-dependent.
6. Microscopic extrathyroidal extension may not be reliably detected on imaging.
7. The study did not evaluate long-term recurrence or disease-specific survival.
8. The cutoff of $\text{NLR} \geq 3.0$ requires validation in an independent population.
9. The numerical findings presented in this draft are illustrative and must be replaced with actual data.

Conclusion

Radiological tumor characteristics, including larger tumor size, multifocality, irregular margins, microcalcifications, extrathyroidal extension, and suspicious cervical lymph nodes, were associated with cervical lymph node metastasis in patients with differentiated thyroid cancer. Histopathological lymphovascular invasion and elevated NLR were also associated with nodal disease. An integrated assessment of ultrasonographic findings, preoperative hematological parameters, and histopathological characteristics may improve risk stratification and clinical planning. However, NLR should be considered an adjunctive marker rather than a standalone diagnostic or prognostic tool. Prospective multicenter studies with larger

samples and long-term follow-up are required to validate these findings.

Declarations

Ethical approval

To be completed according to the actual institutional ethics committee approval.

Consent

Written informed consent should be obtained from all participants before inclusion.

Funding

No external funding was received / to be completed according to the actual study.

Conflict of interest

The authors declare no conflict of interest / to be completed according to the actual study.

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