

Prognostic value of lymph node ratio in metastatic papillary thyroid carcinoma

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Abstract

Objective: Cervical metastases in papillary thyroid carcinoma are associated with increased recurrence. However, their effect on survival remains controversial. This study evaluated literature on the prognostic value of lymph node ratio for loco-regional recurrence and survival in metastatic papillary thyroid carcinoma.

Methods: The PubMed database was systematically searched using the terms ‘papillary thyroid carcinoma’ and ‘lymph node ratio’. Articles addressing the association between lymph node ratio and loco-regional recurrence or survival were identified.

Results: Nine retrospective studies were included, comprising 12 400 post-thyroidectomy and neck dissection papillary thyroid carcinoma patients (median age, 48.6 years; 76 per cent females). Lymph node ratio was associated with worse recurrence-free survival in 60 and 75 per cent of studies investigating the effect of central compartment metastases and both central and lateral compartment metastases on recurrence-free survival, respectively. One large population-based study showed an association between lymph node ratio and disease-specific mortality in N₁ nodal disease, but failed to maintain the same association when N_{1b} patients were excluded.

Conclusion: Regional lymph node ratio is an independent predictor for loco-regional recurrence in pathologically staged N₁ patients with papillary thyroid carcinoma. Patients with a high lymph node ratio should be closely followed up.

Key words: Thyroid Cancer; Carcinoma, Papillary; Lymph Nodes; Neck Dissection; Neoplasm Metastasis

Introduction

Papillary thyroid carcinoma is the most common form of thyroid malignancy, accounting for 60–70 per cent of all thyroid cancer, and occurring more often in women in the fourth and fifth decades of life.¹ Its incidence has more than doubled in the last three decades.² The mortality rate, however, has remained stable with a good prognosis, with a 10-year disease-related survival rate above 90 per cent.^{1–3}

Cervical lymph node metastases are found in 20–50 per cent of cases and in up to 90 per cent when micro-metastases are included. Cervical lymph node metastases are considered an independent risk factor for loco-regional recurrence and increased morbidity.^{4–8} Although cervical metastases are clearly associated with an increased recurrence rate, their effect on survival remains controversial.^{4–8} Mazzaferri and Young found that cervical metastases did not influence survival.⁹ However, other population-based studies demonstrated a negative effect on survival, with varying levels of significance.^{3,10–13}

The current 2016 American Joint Committee on Cancer tumour–node–metastasis (TNM) staging system

for papillary thyroid carcinoma incorporates only the presence and laterality of regional lymph nodes, yet prognosis is affected only in patients older than 45 years. Moreover, it was originally developed to predict risk for mortality rather than recurrence. Although the prognosis of papillary thyroid carcinoma patients with regional disease is quite variable, the American Joint Committee on Cancer TNM staging system does not take into consideration the burden of the metastatic regional disease, and does not differentiate between minimal or extensive metastatic disease in relation to effects on prognosis.

Lymph node ratio is defined as the number of metastatic lymph nodes divided by the number of lymph nodes examined. Lymph node ratio has been shown to be a prognostic variable in non-thyroidal cancers such as head and neck, gastric, breast, and colorectal cancers.^{14–16} In contrast, Roberts *et al.* demonstrated superior prognostic value for the number of positive lymph nodes, in comparison with lymph node ratio and American Joint Committee on Cancer nodal (N) staging for head and neck cancers.¹⁷ Multiple recent studies have evaluated the prognostic value of lymph

node ratio in papillary thyroid carcinoma regarding loco-regional recurrence and survival, with varying results.^{18–26}

This study aimed to review recent publications addressing the prognostic value of lymph node ratio in metastatic papillary thyroid carcinoma.

Materials and methods

A systematic literature review of the PubMed database was conducted on May 2016 using the search terms ‘papillary thyroid carcinoma’ and ‘lymph node ratio’. In addition, we manually searched the references of the identified articles and prior relevant reviews to detect further studies.

All articles that fulfilled our inclusion criteria were included. The studies had to be randomised or non-randomised controlled trials, or prospective or retrospective studies. The participants were post-thyroidectomy and neck dissection papillary thyroid carcinoma patients. There needed to be data regarding central or lateral cervical lymph nodes and lymph node ratio. Positive lymph nodes were required to be confirmed by pathological examination. Sufficient reported data were required for estimating the prognostic value of lymph node ratio on recurrence and survival.

Where available, the following data were extracted for analysis: number of patients, mean number of lymph nodes retrieved, mean number of metastatic lymph nodes, lymph node ratio, lymph node ratio threshold, hazard ratio, prognosis and survival.

This study was approved by the institutional review board of the Chaim Sheba Medical Center, Ramat-Gan, Israel (reference number: 3142-16-SMC).

Results

The electronic search primarily yielded 189 articles. Of these, 164 were excluded on the basis of the title or abstract, resulting in 25 potentially eligible studies. After critical examination, nine studies were considered adequate according to the inclusion criteria.^{18–26}

These nine studies were published between 2012 and 2016. All studies were retrospective. Overall, 12 400 papillary thyroid carcinoma patients were included. All patients had undergone thyroidectomy, and: prophylactic or therapeutic neck dissection; central or lateral compartment neck dissection; or both. Median age at the time of diagnosis was 48.6 years, and 76 per cent of patients were female.

One study utilised the Surveillance, Epidemiology, and End Results database of the National Cancer Institute to evaluate the impact of lymph node ratio in metastatic papillary thyroid carcinoma on disease-related mortality.¹⁸ Eight studies evaluated the prognostic value of lymph node ratio on recurrence-free survival. The patients’ characteristics are summarised in Table I. A significant association was found between lymph node ratio and worse recurrence-free survival in 60 per cent and 75 per cent of the studies that investigated the effect of central compartment metastases

TABLE I
CHARACTERISTICS OF PATIENTS IN IDENTIFIED STUDIES

Characteristic	Jeon <i>et al.</i> ¹⁹	Lang <i>et al.</i> ²⁰	Schneider <i>et al.</i> ²¹	Ryu <i>et al.</i> ²²	Chang <i>et al.</i> ²³	Vas Nunes <i>et al.</i> ²⁴	Park <i>et al.</i> ²⁵	Lee <i>et al.</i> ²⁶
Patients (n)	292	51	69	295	192	198	212	136
Median age (years)	45	45	40	45	46	45	46	51
Female (%)	90	84	59	77	91	66	81	70
Median follow-up duration (months)	96	31	25	88	63	N/A	80	62
Median tumour size (cm)	N/A	2	2.2	1.59	1.1	N/A	N/A	2.1
Recurrence rate (%)	12	8	23	6	8.90	26 (38 persistent, 15 recurrence)	12	19.9
Time to recurrence (months)	N/A	17.3	11.8	20	N/A	N/A	N/A	N/A
Disease-specific mortality rate (%)	0.34	0	N/A	N/A	N/A	N/A	0.47	0
Neck dissection compartment	Central	Central	Central & lateral	Central	Central	Central & lateral	Central & lateral	Central & lateral
Prophylactic &/ or therapeutic neck dissection	Prophylactic & therapeutic	Prophylactic	Therapeutic	Therapeutic	Therapeutic	Prophylactic & therapeutic	Therapeutic	Therapeutic
Number of lymph nodes (median (range))	9 (6–13)	8 (3–26)	20 (3–94)	7 (1–30)	7 (1–38)	N/A	31.4	48 (12–144)
Number of positive lymph nodes (median (range))	3 (2–5.5)	4 (1–16)	4 (0–29)	2 (1–15)	2 (1–15)	N/A	N/A	10 (1–48)
Median total LNR	N/A	N/A	0.35	N/A	N/A	N/A	N/A	0.2
Median central LNR	0.3	0.57	0.45	0.44	0.5	N/A	N/A	N/A

N/A = not available; LNR = lymph node ratio

and both central and lateral compartment metastases on recurrence-free survival, respectively.^{19–26} Different lymph node ratio thresholds were used in each study (range, 0.3–0.86). The prognostic values of lymph node ratio and the hazard ratios for loco-regional recurrence are presented in Table II.

Discussion

Cervical lymph node metastases are found in 20–50 per cent of papillary thyroid carcinoma patients and in up to 90 per cent when including micro-metastases. The current American Joint Committee on Cancer TNM staging system for papillary thyroid carcinoma incorporates only the presence and laterality of regional lymph nodes, and does not take into consideration the burden of metastatic regional disease. Lymph node ratio may have greater prognostic value, as it takes into consideration both the extent of surgery and the regional metastatic burden. Thus, it can differentiate between minimal and extensive metastatic disease, an issue missing from the American Joint Committee on Cancer TNM classification.

Although the data on the extent of nodal involvement and its subsequent effect on disease recurrence and overall survival rates are still debated, previous studies have demonstrated that cervical lymph node metastasis is correlated with loco-regional papillary thyroid carcinoma recurrence.^{4–8} Even though the lymph node ratio has prognostic significance in several non-thyroidal cancers, its significance in papillary thyroid carcinoma remains unclear.^{14–17} This study focused on the regional lymph node ratio in metastatic papillary thyroid carcinoma, and considered its prognostic significance on loco-regional recurrence and survival.

Only one study investigated the effect of lymph node ratio on survival. Schneider *et al.* utilised a population-level database (the Surveillance, Epidemiology, and End Results database) of the National Cancer Institute, and identified 10 955 metastatic papillary thyroid carcinoma patients treated with thyroidectomy and neck dissection.¹⁸ Those authors demonstrated a significant association between lymph node ratio and disease-related mortality, with a hazard ratio of 4.33 (95 per cent confidence interval (CI) = 1.68–11.18, $p < 0.01$); there was a significant increase in disease-related mortality from 0.65 per cent for patients with a lymph node ratio of less than 0.42 to 1.72 per cent for patients with a lymph node ratio of 0.42 or more ($p < 0.01$). Yet, this association lost its significance when the analyses were performed after excluding patients with N_{1b} disease, raising the question of whether the significance of lymph node ratio on survival may be attributed to lateral neck disease alone.

Central compartment analysis

Five out of eight studies^{19–22,24} investigated the effect of central compartment metastases (N_{1a}) alone on recurrence. Three of the studies^{19,21,22} (60 per cent)

TABLE II
LYMPH NODE RATIOS AND HAZARD RATIOS FOR RECURRENCE-FREE SURVIVAL IN IDENTIFIED STUDIES

Parameter	Jeon <i>et al.</i> ¹⁹	Lang <i>et al.</i> ²⁰	Schneider <i>et al.</i> ²¹	Ryu <i>et al.</i> ²²	Chang <i>et al.</i> ²³	Vas Nunes <i>et al.</i> ²⁴	Park <i>et al.</i> ²⁵	Lee <i>et al.</i> ²⁶
Median total LNR	N/A	N/A	0.35	N/A	N/A	N/A	N/A	0.2
Median central LNR	0.3	0.57	0.45	0.44	0.5	N/A	N/A	N/A
LNR threshold	0.4	Group 1 = 0–0.33; group 2 = 0.34–0.66; group 3 = >0.67	0.7 total LNR; 0.86 central LNR	0.65	0.48	0.3	0.22	0.26
Hazard ratio	14.83	N/A	19.5	N/A	N/A	3.2	N/A	N/A
Recurrence-free survival rate (below threshold vs above threshold) (%)	N/A	N/A	N/A	98.6% vs 75.4% (10-year)	N/A	N/A	97.1% vs 78.8% (5-year)	N/A
Prognostic value for RFS	Significant	Not significant	Significant	Significant	Not significant	Significant	Significant	Not significant

LNR = lymph node ratio; N/A = not available; RFS = recurrence-free survival

found a significant association between lymph node ratio and recurrence-free survival on multivariate analysis.

Jeon *et al.* investigated 292 papillary thyroid carcinoma patients who underwent prophylactic (63 per cent) or therapeutic (37 per cent) central neck dissection.¹⁹ The median numbers of retrieved and metastatic lymph nodes were 9 (range, 6–13) and 3 (range, 2–5.5), respectively. The hazard ratio for recurrence in their study population increased significantly from 2.92 (95 per cent CI = 0.88–9.76, $p = 0.081$) in patients with a lymph node ratio of less than 0.4 to 14.83 (95 per cent CI = 5.07–43.35, $p < 0.001$) in patients with a lymph node ratio of 0.4 or more. They also found that lymph node ratio had a more distinct effect on prognosis as compared to lymph node size.

Lang *et al.* conducted their study on 51 clinically staged N₀ papillary thyroid carcinoma patients who underwent unilateral prophylactic central neck dissection.²⁰ The median numbers of retrieved and metastatic lymph nodes were 8 (range, 3–26) and 4 (range, 1–16), respectively. They found that lymph node ratio was associated with higher post-ablative thyroglobulin levels, which may lead to a greater recurrence rate. However, no direct association between lymph node ratio and recurrence-free survival was found. This is the only study to investigate the prognostic value of lymph node ratio in patients with clinically staged N₀ disease.

In a study, by Schneider *et al.*, of 69 patients who underwent therapeutic neck dissection for N₁ disease, 35 patients (50.7 per cent) underwent therapeutic central neck dissection for N_{1a} disease.²¹ Only lymph node ratio was significantly associated with recurrence on multivariate analysis, with an average hazard ratio of 19.5 (95 per cent CI = 4.1–22.9, $p < 0.01$) in patients with a central lymph node ratio of 0.86 or more.

Ryu *et al.* showed that a central lymph node ratio of 0.65 or more was the only independent variable predictive for recurrence in a multivariate analysis of 295 patients with N_{1a} papillary thyroid carcinoma who underwent thyroidectomy and bilateral central neck dissection.²² They found no association between recurrence-free survival and tumour size, multi-centricity, thyroiditis and total number of positive lymph nodes. The 10-year estimated recurrence-free survival rates were 98.6 per cent and 75.4 per cent for patients with lymph node ratios of less than 0.65 and 0.65 or more, respectively. The median numbers of retrieved and metastatic lymph nodes were 7 (range, 1–30) and 2 (range, 1–15), respectively.

Chang *et al.* investigated 192 patients with metastatic papillary thyroid carcinoma who underwent therapeutic central neck dissection.²³ The median numbers of retrieved and metastatic lymph nodes were 7 (range, 1–38) and 2 (range, 1–15), respectively. Multivariate analysis showed that a lymph node ratio of 0.48 or more was not an independent risk factor for recurrence. Instead, they found that maximal size of

metastatic foci, American Thyroid Association risk categories and stimulated serum thyroglobulin levels were predictive of recurrence after surgery. A pre-ablation thyroglobulin level of 9.3 ng/ml or higher was an independent risk factor for recurrence.

Central and lateral compartment analysis

Four out of eight studies^{21,24–26} did not differentiate between N_{1a} and N_{1b} patients when investigating the effect of lymph node ratio on recurrence-free survival. Three of these studies (75 per cent) found a significant association between lymph node ratio and recurrence-free survival on multivariate analysis.

As mentioned above, Schneider *et al.* conducted a study that included 69 patients who underwent therapeutic neck dissection for N₁ disease (34 patients underwent central and lateral neck dissection).²¹ The median numbers of retrieved and metastatic lymph nodes were 20 (range, 3–94) and 4 (range, 0–29), respectively. A lymph node ratio of 0.7 or higher was the only significant risk factor for recurrence on multivariate analysis, with a hazard ratio of 19.5 (95 per cent CI = 4.1–22.9, $p < 0.01$). All other prognostic factors, including age, gender, tumour size, multifocality, extrathyroid extension, lymphovascular invasion, extranodal extension and radioactive iodine, failed to predict recurrence on multivariate analysis.

In a study, by Vas Nunes *et al.*, of 198 patients with papillary thyroid carcinoma undergoing prophylactic and therapeutic neck dissection, 60 per cent of the patients had central compartment dissection, and 40 per cent had either lateral compartment dissection or both central and lateral compartment dissection.²⁴ Lymph node ratio was associated with a decrease in recurrence-free survival, with a hazard ratio of 3.2 (95 per cent CI = 1.4–7.3, $p = 0.005$). Patients with a lymph node ratio of 0.3 or more had a 3.4 times higher risk of persistent or recurrent disease compared to patients with a lymph node ratio of 0, while patients with a lymph node ratio of 0.11 or less had an 80 per cent chance of remaining disease-free over five years.

Park *et al.* found that loco-regional recurrence-free survival was significantly decreased in patients with more than six metastatic lymph nodes and a lymph node ratio of more than 0.22.²⁵ The five-year recurrence-free survival rate for patients with a lymph node ratio of 0.22 or less or a ratio of more than 0.22 was 97.1 per cent and 78.8 per cent, respectively. Their study involved 212 papillary thyroid carcinoma patients with N_{1b} disease. The average number of removed lymph nodes per patient was 31.4.

Lee *et al.* recently published a study on the prognostic value of the lymph node ratio of lateral compartment metastases in papillary thyroid carcinoma on loco-regional recurrence.²⁶ They failed to show a significant association between lymph node ratio and recurrence-free survival in 136 patients with papillary thyroid carcinoma and clinically staged N_{1b} disease who underwent thyroidectomy with therapeutic central and lateral

neck dissection. However, other prognostic factors, such as largest size of metastatic lymph node, American Thyroid Association risk categories, and stimulated thyroglobulin level, were independent predictive factors of recurrence-free survival on multivariate analysis. The median numbers of dissected and positive lymph nodes were 48 (range, 12–144) and 10 (range, 1–48), respectively.

General discussion

As papillary thyroid carcinoma is an indolent tumour with an excellent prognosis, it is difficult to adequately evaluate the prognostic significance of lymph node ratio on survival unless data from a large patient population followed for a long period are available for analysis. Only one study investigated the effect of lymph node ratio on disease-specific mortality.¹⁸

Prophylactic central neck dissection in clinically staged N₀ papillary thyroid carcinoma patients is still controversial. Lang *et al.* showed no association between lymph node ratio and loco-regional recurrence in 51 patients with clinically staged N₀ disease.²⁰ A larger cohort is required to better understand the effect of central compartment micro-metastasis on prognosis.

While the majority of the studies reviewed showed a positive association between lymph node ratio and higher loco-regional recurrence on multivariate analysis, many of these studies failed to show a significant association between recurrence and some of the popular prognostic factors used today, such as the American Joint Committee on Cancer TNM staging system, tumour size, extrathyroid extension, age or gender. This may indicate the need for a new staging system for papillary thyroid carcinoma that incorporates regional metastatic burden in its classification system, to better evaluate recurrence risk in patients with pathologically staged N₁ disease. Patients with a higher lymph node ratio should be considered ‘high risk’ for loco-regional recurrence and should be monitored closely during follow up. Early detection of recurrence may lead to effective and overall better management.

We recognise several significant drawbacks in our review. All studies were retrospective, and the majority did not differentiate between therapeutic and prophylactic neck dissections, or between central and lateral compartment analysis. All studies but one included a relatively small number of patients and short follow-up periods, limiting the studies’ ability to assess the relationship between lymph node ratio and disease-related survival. Lymph node ratio is affected by the extent of surgery (number of lymph nodes retrieved) and by the enthusiasm of the pathologist, which may greatly alter the result of lymph node ratio. Furthermore, the extent and dosage of radioactive iodine used post-operatively was not included in the multivariate analysis in the majority of the studies.

Future prospective studies examining the relationship of lymph node ratio to recurrence and survival

should take into account the laterality of the lymph nodes, their size, and the distinction between micro- and macro-metastases.

Conclusion

Regional lymph node ratio in papillary thyroid carcinoma patients with pathologically staged N₁ disease was an independent predictor for loco-regional recurrence in 60 per cent and 75 per cent of the studies that investigated the effect of central compartment metastases and both central and lateral compartment metastases on recurrence-free survival, respectively. Many of the well-accepted prognostic factors, such as the American Joint Committee on Cancer TNM classification, extra-thyroidal extension, age and gender, failed to predict recurrence on multivariate analysis in many of the studies. A newer classification system that incorporates lymph node ratio as a prognostic factor for recurrence should be considered.

A high lymph node ratio should encourage clinicians to closely follow up metastatic papillary thyroid carcinoma patients. Based on this review, we recommend the close follow up of patients with a lymph node ratio of more than 0.3 in both central and lateral compartment metastases because of the increased risk for recurrence. Lymph node recurrence in the lateral compartment only had an effect on survival. As not all studies reached statistical significance for the association between lymph node ratio and recurrence, large randomised controlled studies should be conducted to better elucidate the prognostic value of the lymph node ratio in metastatic papillary thyroid carcinoma.

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