Short Communication

Prognostic Value of Lymph Node Ratio in Metastatic Papillary Thyroid Carcinoma

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Abstract

Objective: Cervical metastasis in Papillary Thyroid Carcinoma (PTC) has a clear association with an increased recurrence rate. However, its effect on survival remains controversial. The purpose of this study was to evaluate the recent publications regarding the prognostic value of Lymph Node Ratio (LNR) on loco-regional recurrence and survival in metastatic PTC.

Methods: A systematic literature search of PubMed databases for relevant articles was conducted on May 2016. The following search terms were applied: PTC and LNR. All articles addressing the association between LNR and loco-regional recurrence or survival were included.

Results: 10 retrospective studies were included. Overall, 12,653 post thyroidectomy and neck dissection PTC patients were included. Median age was 48.4 years and 77% were females. Six out of nine studies showed association between LNR and worse recurrence-free survival with variable levels of significance and LNR thresholds. The other 3 studies did not show any association between LNR and recurrence. One large population-based study showed significant association between LNR and disease-specific mortality in N1 (AJCC TNM) disease but failed to maintain the same association when N1b patients were excluded.

Conclusions: Regional LNR in PTC with pathological N1 patients is an independent predictor for loco-regional recurrence. High LNR should alert clinicians to closely follow-up these patients.

INTRODUCTION

Papillary Thyroid Carcinoma (PTC) is the most common form of thyroid malignancy and accounts for 60% to 70% of all thyroid cancer, occurring more often in women in the 4th and 5th decades [1]. Its incidence has more than doubled in the last three decades [2]. Mortality rate however, has remained stable with good prognosis with a 10-year disease-related survival above 90% [1-3]. Cervical lymph node metastasis is found in 20%-50% of cases and up to 90% when micro-metastasis of PTC are included. Cervical lymph node metastases are considered an independent risk factor for loco-regional recurrence and increased morbidity [4-8]. Although cervical metastasis has a clear association with an increased recurrence rate, its effect on survival remains controversial [4-8] Young et al. [9], found that cervical metastases did not influence survival. However, other population-based studies demonstrated a negative effect on survival with varying levels of significance [3,10-12,17]. The current AJCC TNM staging system for PTC incorporates only the presence and laterality of regional LNs, 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 prognosis of PTC patients with regional disease is quite variable, AJCC TNM staging system does not take into consideration the burden of the metastatic regional disease nor differentiates between a minimal or extensive metastatic disease and its effect on prognosis. Lymph Node ratio (LNR) is defined as the number of metastatic lymph nodes divided by number of lymph nodes examined. LNR 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, Vasu Divi et al. [17], demonstrated superior prognostic value for the number of positive lymph nodes in comparison with the LNR and AJCC N staging for head and neck cancers. Multiple studies were published evaluating the prognostic value of LNR in PTC regarding loco-regional recurrence and survival with varying results [18-27]. The purpose of this study was to review recent
publications addressing the prognostic value of LNR in metastatic PTC.

**METHODS**

A systematic literature review of PubMed® databases for relevant articles was conducted on May 2016 using the following search terms: papillary thyroid carcinoma and lymph node ratio. In addition, we manually searched the references of the identified articles and prior relevant reviews. All articles which fulfilled our inclusion criteria were included: (1) the studies had to be randomized or nonrandomized controlled trials or prospective or retrospective studies; (2) the participants were post thyroidectomy and neck dissection PTC patients; (3) there was data about central or lateral cervical lymph nodes and lymph node ratio; (4) positive lymph nodes were confirmed by pathologic examination; (5) and sufficient data was reported for estimating the prognostic value of LNR on recurrence and survival. When available, the following data was extracted for analysis; number of patients, LNR, LNR threshold, hazard ratio, prognosis and survival.

This study was approved by the Institutional review board of the Chaim Sheba Medical Center (3142-16-SMC).

**RESULTS**

The electronic search primarily yielded 189 articles. Of these, 164 were excluded on the basis of the title or abstract, leading to 25 potentially eligible studies. After critical examination, 10 studies were considered adequate according to the inclusion criteria [18-27]. These studies were published between 2012 and 2016. All studies were retrospective. Overall, 12,653 PTC patients were included. All patients had undergone thyroidectomy and either prophylactic or therapeutic neck dissection; central or lateral compartment or both. Median age at the time of diagnosis was 48.4 years and 77% were females. Patient’s characteristics are summarized in (Table 1). One study utilized the Surveillance, epidemiology, and end results (SEER) database of the National Cancer Institute to evaluate the impact of LNR in metastatic PTC on disease-related mortality (DRM) [17]. The other nine studies evaluated the prognostic value of LNR on Recurrence-free survival (RFS); 6 studies demonstrated that LNR had a significant prognostic value in association with worse RFS in patients with higher LNR on multivariate analysis, though different LNR thresholds were used in each study (0.2-0.8) [19,21-24,26]. Nonetheless, three studies failed to demonstrate a significant association between LNR and RFS on multivariate analysis [18,26,28]. Prognostic value of LNR and the hazard ratios for loco-regional recurrence are presented in (Table 2).

**DISCUSSION**

Cervical lymph node (LN) metastases are found in 20%-50% of cases of PTC and up to 90% when including micro-metastasis. The current AJCC TNM staging system for PTC incorporates only the presence and laterality of regional LNs and doesn’t take into consideration the burden of metastatic regional disease. LNR may have a greater prognostic value since it takes into consideration both the extent of surgery as well as the regional metastatic burden. Thus, it can differentiate between minimal and extensive metastatic disease, an issue missing from the AJCC TNM classification. Although the data on the extent of nodal involvement and its subsequent effect on recurrence of disease

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Number of Patients</th>
<th>Median Age (years)</th>
<th>Female (%)</th>
<th>Median Follow-up months</th>
<th>Median tumor size</th>
<th>Recurrence (%)</th>
<th>Time to recurrence (months)</th>
<th>Disease-specific Mortality (%)</th>
<th>Neck dissection Compartment</th>
<th>Prophylactic/Therapeutic Neck Dissection</th>
<th>Median lymph node number</th>
<th>Median number of positive lymph nodes</th>
<th>Median LNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lo et al. [18]</td>
<td>51</td>
<td>45</td>
<td>84%</td>
<td>31</td>
<td>2</td>
<td>8%</td>
<td>17.3</td>
<td>0%</td>
<td>Central</td>
<td>Prophylactic</td>
<td>7.9</td>
<td>4.47</td>
<td>0.57</td>
</tr>
<tr>
<td>Kim et al. [19]</td>
<td>292</td>
<td>45</td>
<td>90%</td>
<td>96</td>
<td>NA</td>
<td>12%</td>
<td>NA</td>
<td>0.34%</td>
<td>Central</td>
<td>Prophylactic &amp; Therapeutic</td>
<td>9</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>Sippel et al. [20]</td>
<td>69</td>
<td>40</td>
<td>59%</td>
<td>25</td>
<td>NA</td>
<td>23%</td>
<td>NA</td>
<td>NA</td>
<td>Central &amp; Lateral</td>
<td>Therapeutic</td>
<td>20</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>Kim et al. [22]</td>
<td>295</td>
<td>45</td>
<td>77%</td>
<td>88</td>
<td>1.59</td>
<td>6%</td>
<td>20</td>
<td>0%</td>
<td>Central &amp; Lateral</td>
<td>Therapeutic &amp; Therapeutic</td>
<td>8.1</td>
<td>2.8</td>
<td>NA</td>
</tr>
<tr>
<td>Walfish et al. [23]</td>
<td>253</td>
<td>47</td>
<td>75%</td>
<td>68</td>
<td>NA</td>
<td>14%</td>
<td>20</td>
<td>0%</td>
<td>Central &amp; Lateral</td>
<td>Therapeutic &amp; Therapeutic</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Elliott et al. [24]</td>
<td>198</td>
<td>45</td>
<td>66%</td>
<td>NA</td>
<td>NA</td>
<td>14%</td>
<td>11.8</td>
<td>0%</td>
<td>Central</td>
<td>Therapeutic</td>
<td>1.1</td>
<td>NA</td>
<td>0.36</td>
</tr>
<tr>
<td>Son et al. [25]</td>
<td>192</td>
<td>46</td>
<td>91%</td>
<td>NA</td>
<td>NA</td>
<td>26%</td>
<td>17.3</td>
<td>0%</td>
<td>Central &amp; Lateral</td>
<td>Therapeutic</td>
<td>1.5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lee et al. [26]</td>
<td>212</td>
<td>46</td>
<td>81%</td>
<td>NA</td>
<td>NA</td>
<td>26%</td>
<td>20</td>
<td>0%</td>
<td>Central &amp; Lateral</td>
<td>Therapeutic</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kim et al. [27]</td>
<td>136</td>
<td>51</td>
<td>70%</td>
<td>NA</td>
<td>NA</td>
<td>26%</td>
<td>NA</td>
<td>0.47%</td>
<td>Central &amp; Lateral</td>
<td>Therapeutic &amp; Therapeutic</td>
<td>2</td>
<td>NA</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Table 1: Patient characteristics among nine studies.**
and overall survival rates are still debated, previous studies demonstrated that cervical LN metastasis correlated with loco-regional recurrence of PTC [4-8]. Although LNR bears prognostic significance in several non-thyroidal cancers, its significance in PTC remains unclear [14-17]. This study focused on regional lymph node ratio in metastatic papillary thyroid carcinoma and its prognostic significance on the loco-regional recurrence and survival.

Only one study investigated the effect of LNR on survival. Sippel et al. [17], utilized population level database (SEER) of the National Cancer Institute with 10,955 metastatic PTC patients who were treated with thyroidectomy and neck dissection. They demonstrated a significant association between LNR and DRM with a hazard ratio of 4.33 (95% CI; 1.68-11.18, p < 0.01); resulting in an increased DRM of 1.72% for patients with LNR ≥ 0.42 compared to a DRM of 0.65% for patients with LNR < 0.42 (p<0.01). Yet, this association lost its significance when the analysis was performed after excluding patients with N1b disease, raising the question whether the significance of LNR on survival may be attributed to lateral neck disease alone. Six studies showed significant association between LNR and worsening of RF Son multivariate analysis. Different LNR thresholds were calculated in each study with variable effect. Kim et al. [19], investigated 292 PTC patients who underwent prophylactic or therapeutic central neck dissection. The hazard ratio for recurrence in their study population for patients with LNR ≥ 0.4 and LNR < 0.4 was 14.83 (95% CI; 5.07-43.35, p<0.001) and 2.92 (95% CI; 0.88-9.76, p=0.081), respectively. They also found that LN ratio has a more distinct effect on prognosis as compared to LN size. Sippel et al. [21], conducted a study on 69 patients who underwent therapeutic neck dissection for N1 disease. LNR was significantly associated with recurrence with an average odds ratio of 19.5 (95% CI; 4.1-72.9, p<0.01) in patients with total LNR ≥ 0.7 and central LNR ≥ 0.86. Walfish et al. [23], published his results on 253 PTC patients who had central or lateral therapeutic neck dissection. LNR independently predicted PTC recurrence with odds ratio of 1.024 (95% CI; 1.010-1.039, p = 0.001). They found that the addition of LNR to the classical TNM classification yielded a greater accuracy in predicting PTC recurrence than did TNM classification alone. Elliott et al. [24] conducted a study on 198 patients with PTC undergoing thyroid surgery and neck dissection, both prophylactic and therapeutic. LNR was associated with a decrease in recurrence-free survival with a hazard ratio of 3.2 (95% CI; 1.4-7.3, p = 0.005). Patients with LNR ≥ 0.3 had a 3.4 times higher risk of persistent or recurrent disease compared to patients with LNR of 0, while patients with LNR ≤ 0.11 had an 80% chance of remaining disease free during 5 years. Lee et al. [26], found that loco-regional recurrence-free survival was significantly decreased in patients with > 6 metastatic lymph nodes and lymph node ratio > 0.22. Their study involved 212 PTC patients with N1b disease. Lo et al. [18], conducted their study on 51 PTC patients with clinicalN0 (cN0) who underwent unilateral prophylactic central neck dissection. They found that LNR was associated with higher rate of post-ablative Thyroglobulin levels, which may imply higher future recurrence rate. However, no direct association between LNR and recurrence-free survival was found. This is the only study to investigate the prognostic value of LNR in patients with cN0 disease. Son et al. [25], published a study involving 192 patients with metastatic PTC who underwent therapeutic central neck dissection. Multivariate analysis showed that a LNR value of ≥ 0.48 was not an independent risk factor for recurrence. On the other hand, a pre-ablation Thyroglobulin level value of ≥ 9.3 ng/mL was an independent risk factor for recurrence. Kim et al. [22,27], recently published two studies on the prognostic value of LNR of central or lateral compartment metastasis in PTC on loco-regional recurrence. They showed that central LNR ≥ 0.65 is the only independent variable for recurrence in multivariate analysis in 295 patients with N1a PTC who underwent thyroidectomy and bilateral central neck dissection [22]. The 10-year estimated recurrence-free survival rates were 98.6% for patients with LNR < 0.65 and 75.4% for patients with LNR ≥ 0.65. However, they failed to show a significant association between LNR and RFS in 136 patients with PTC and clinical N1b disease who underwent thyroidectomy with therapeutic central and lateral neck dissection [27]. Instead they found that maximal size of metastatic foci, ATA risk categories and stimulated serum Thyroglobulin levels are predictive of recurrence after surgery. Only one study investigated the effect of LNR on disease-specific mortality. Since PTC is an indolent tumor with an excellent prognosis, it is difficult to adequately evaluate the prognostic significance on survival of LNR unless a large patient population followed for a long period is available for analysis.

Propylactic Central Neck dissection in cN0 PTC is still controversial. Lo et al. [15], showed no association with LNR.

Table 2: LNR Hazard Ratio for recurrence-free survival among nine studies.

<table>
<thead>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Total LNR</td>
<td>NA</td>
<td>NA</td>
<td>0.35</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Median Central LNR</td>
<td>0.57</td>
<td>0.3</td>
<td>0.45</td>
<td>0.44</td>
<td>NA</td>
<td>NA</td>
<td>0.5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>LNR threshold</td>
<td>Group 1: 0-0.33, Group 2: 0.34-0.66, Group 3: &gt;0.67</td>
<td>0.4</td>
<td>0.7 (total LNR), 0.86 (central LNR)</td>
<td>0.65</td>
<td>NA</td>
<td>0.3</td>
<td>0.48</td>
<td>0.22</td>
<td>0.26</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>NA</td>
<td>14.83</td>
<td>19.5</td>
<td>NA</td>
<td>1.024</td>
<td>3.4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Recurrence-free survival (Below threshold vs Above threshold) NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>98.6% vs 75.4% (10-year)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>97.1% vs 78.8% (5-year)</td>
<td>NA</td>
</tr>
<tr>
<td>Prognostic Value for RFS Not significant</td>
<td>Significant</td>
<td>Significant</td>
<td>Significant</td>
<td>Significant</td>
<td>Significant</td>
<td>Significant</td>
<td>Not significant</td>
<td>Significant</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

and loco-regional recurrence in 51 patients with cN0 disease. A larger study needs to be conducted to better understand the effect of central compartment micro-metastasis on prognosis. On the one hand, the majority of the studies reviewed showed a positive association between LNR and higher loco-regional recurrence on multivariate analysis. On the other hand, these studies failed to show a significant association between recurrence and some of the popular prognostic factors used today such as AJCC TNM staging system, tumor size, extra-thyroid extension, age or gender on multivariate analysis. This may indicate the need for a new staging system for PTC which incorporates regional metastatic burden in its classification system to better evaluate recurrence risk in patients with pathological N1 (pN1) disease. Patients with higher LNR 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 recognize several significant drawbacks in our report. All studies were retrospective and the majority did not differentiate between therapeutic and prophylactic neck dissection or between central and lateral compartment analysis. All studies but one included a relatively small number of patients and short follow-up period limiting the studies’ ability to assess the relationship between LNR and disease-related survival. LNR is affected by the extent of surgery (number of LNs retrieved) and by the enthusiasm of the pathologist. Both of these factors may greatly alter the result of LNR. Furthermore, the extent and dosage of radioactive iodine used postoperatively was not included in the multivariate analysis. Future prospective studies examining the relationship of LNR to recurrence and survival should take into account the laterality of the lymph nodes, their size and the distinction between micro and macro metastasis.

CONCLUSIONS

Regional LNR in PTC with pN1 patients is an independent predictor for loco-regional recurrence out of nine studies. Many of the well-accepted prognostic factors such as AJCC TNM classification, extra thyroid extension, age or gender failed to predict recurrence on multivariate studies in some of the studies. A newer classification should be considered to incorporate LNR as a prognostic factor for recurrence. High LNR should promote clinicians to closely follow-up patients with metastatic PTC. Large randomized controlled studies should be conducted to give a better perspective on the prognostics value of LNR in metastatic PTC.

REFERENCES


