Predictors of Lateral Cervical Lymph Node Metastases in Differentiated Thyroid Cancer

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Abstract

Background: Some studies have shown that the addition of a lateral neck nodal dissection to central neck compartment surgery doubles the risk of transient postoperative hyperparathyroidism. The aim of this study was to evaluate predictors of patients with differentiated thyroid cancer who have lateral cervical lymph node metastasis and need lateral neck nodal dissection.

Patients and Methods: This is a retrospective study which will include all patients who had undergone thyroidectomy for differentiated thyroid cancer at South Egypt Cancer Institute between Jan. 2010 to Dec. 2014. The following factors will be analyzed to detect the most important predictors of lateral cervical lymph node metastasis: primary tumor size, age, sex, thyroid capsular invasion, multifocality of primary disease, histological type and clinical and radiological evidence of lymph node involvement.

Results: The study included 69 patients with well differentiated thyroid cancer who were managed at Surgical Oncology Department, South Egypt institute from Jan. 2010-Dec. 2014. 16 patients were males (23.19%) and 53 females (76.81%) A mean (SD) age of 42.71 years. A median of 41 years (range: 10-78). 44 patients (63.77%) with papillary thyroid cancer, 15 patients (21.74%) with follicular variant of papillary thyroid cancer, and 10 patients (14.49%) with follicular thyroid cancer. Capsular invasion detected in 29 patient (45.31%) while no invasion in 35 patients (54.69%). Clinically 41 patients (59.42%) don’t have LN involvement and 28 patients (40.58%) show LN involvement, by neck U/S 43 patients (62.32%) don’t have LN involvement and 26 patients (37.68 %) show L.N. involvement.

Conclusion: Positive clinical examination and U/S neck examination are the most dependent and reliable factors to detect lateral cervical lymph node involvement, which indicate lateral cervical lymph node dissection.

Key Words: Lateral cervical lymph node – Thyroid cancer.

Introduction

CANCER of the thyroid gland is the most common malignant disease of the endocrine system. It accounts approximately for 1% of human malignancies. The majority of cases (approximately 70%) occur in females and it is the seventh most common cancer affecting women. Differentiated Thyroid Carcinoma (DTC) is the most common form of thyroid malignancy, accounting for about 90% of all cases, and includes Papillary Thyroid Cancer (PTC) and Follicular Thyroid Cancer (FTC) [1].

Cervical (regional) lymph node metastases from Differentiated Thyroid Cancer (DTC) are very common, particularly in patients with Papillary Thyroid Cancer (PTC). Depending on the detection method employed, 30%-80% of patients with PTC harbor lymph node metastases, mostly in the central neck [2,3].

Nodal disease increases the risk of recurrence, especially when lymph node metastases are macroscopic; the impact of microscopic lymph node metastases on recurrence and survival is less clear [4,5].

Optimizing the surgical approach is fundamental to appropriate initial management of DTC and involves balancing the risks and benefits of thyroidectomy and neck dissection [6,7].

Because DTC is more indolent than squamous cell carcinoma metastatic to the lymph nodes of the neck, it is not possible to universally extrapolate from one disease to the other. Regional lymph node spread from thyroid cancer can broadly be classified as central neck compartment and lateral neck compartment metastases. Lymph node metastases are most commonly found in the central neck compartment (level VI and level VII) [8].
Although less frequent, metastases to lymph nodes in the lateral neck, levels I-V may be associated with a worse prognosis [9]. There is a clear-association between central neck involvement and the likelihood of lateral neck disease, as an increase in the number of positive central neck lymph nodes is associated with a higher incidence of lateral neck disease [10].

The more extensive dissection required for lateral neck lymph node metastases is associated with cosmetic concerns, such as a longer incision, and the potential for nerve injury (marginal mandibular, accessory, sympathetic, phrenic, vagus, hypoglossal, cervical sensory branches, brachial plexus, and greater auricular nerves), hemorrhage, and chyle leak that are not associated with thyroidectomy alone with or without central neck dissection [11,12]. Complications from lateral neck dissections can be as high as 50%, with a 3.6% incidence of chyle leak and an 11% or more incidence of chronic neck pain and numbness. Some studies show that the addition of a lateral neck nodal dissection to central neck compartment surgery (thyroidectomy or central neck nodal dissection) doubles the risk of transient postoperative hypoparathyroidism [13].

Patients and Methods

A- Nature of study:

This study is a retrospective one; which will include all patients who had underwent thyroidectomy for well differentiated thyroid cancer at South Egypt Cancer institute between Jan. 2010 to Dec. 2014.

B- Method:

The study will detect the impact of different factors on lateral lymph node metastasis as:

- Primary tumor size.
- Age.
- Sex.
- Thyroid capsular invasion.
- Multifocality of primary disease.
- Histological type.
- Clinical and radiological evidence of lymph node involvement.

Analyzing these factors will help to select patients who have high risk of lymph node metastasis and need lateral neck nodal dissection.

C- Inclusion criteria:

- All patients with well differentiated thyroid cancer admitted to South Egypt Cancer Insti-

tute during the study period and underwent surgery with available pathology report with sufficient data.

- All age groups.

D- Data collection:

From patient file and computerized data then statistical analysis was performed using STATA intercooled version 9.2. Quantitative data was analyzed using Mann-Whitney test was used as the data was not normally distributed.

Qualitative data was compared using Chi square test. Univariate and multivariate logistic regression analysis were done to detect factors that predict LN involvement.

- value was considered significant if it was less than 0.05.

E- Ethical considerations:

The study is accepted by our local committee.

Results

This study included 69 patients with well differentiated thyroid cancer who were managed at South Egypt Institute from Jan. 2010-Dec. 2014.

Patients' characteristics:

Gender: Patients were 16 males (23.19%) and 53 females (76.81%).

Age: A mean (SD) age of 42.71 years. A median of 41 years (range: 10-78).

Table (1) shows a comparison between those with and without LN involvement according to age and sex of patients.

Pathology:

They were 44 patients (63.77%) with papillary thyroid cancer, 15 patients (21.74%) with follicular variant of papillary thyroid cancer, and 10 patients (14.49%) with follicular thyroid cancer.

Size: A mean (SD) size of the lesion 2.85cm. A median of 2cm (range 0.1-11cm).

Invasion of the capsule: Patient with well differentiated thyroid cancer invading the capsule were 29 patient (45.31%) and those with no invasion were 35 patients (54.69%).

Multifocal tumor: Patient who have multifocal tumor were 19 patient and those with no multifocal tumor 44 (69.84%).
Table (1) shows a comparison between those with and without LN involvement according to Characteristics of tumors.

Table (1): Comparison between patients with and without L.N. involvement according to the tumour characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lymph node involvement</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (N=47)</td>
<td>Yes (N=22)</td>
</tr>
<tr>
<td><strong>Pathology:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>28 (59.57%)</td>
<td>16 (72.73%)</td>
</tr>
<tr>
<td>Follicular variant of</td>
<td>11 (23.40%)</td>
<td>4 (18.18%)</td>
</tr>
<tr>
<td>papillary follicular</td>
<td>8 (17.02%)</td>
<td>2 (9.09%)</td>
</tr>
<tr>
<td><strong>Size:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.76 (2.63)</td>
<td>3.04 (2.99)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2 (0.1-11)</td>
<td>1.75 (0.5-9)</td>
</tr>
<tr>
<td><strong>Size:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>18 (41.86%)</td>
<td>10 (50.00%)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>25 (58.14%)</td>
<td>10 (50.00%)</td>
</tr>
<tr>
<td><strong>Capsular invasion:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28 (60.87%)</td>
<td>7 (38.89%)</td>
</tr>
<tr>
<td>Yes</td>
<td>18 (39.13%)</td>
<td>11 (61.11%)</td>
</tr>
<tr>
<td><strong>Multifocality:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>35 (76.09%)</td>
<td>9 (52.94%)</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (23.91%)</td>
<td>8 (47.06%)</td>
</tr>
</tbody>
</table>

By clinical examination: 41 patients (59.42%) don’t have L.N. involvement and 28 patients (40.58%) show L.N. involvement.

By neck U/S: 43 patients (62.32%) don’t have L.N. involvement and 26 patients (37.68%) show L.N. metastasis. Table (2) shows a comparison between those with and without LN involvement according to clinical picture and radiology of tumor:

Postoperative pathology: Patient who don’t have L.N. involvement were 47 patients (68.12%) and those with L.N. involvement 22 patient (31.88%).

Patient who underwent neck dissection were 43 (62.32%) of whom only 21 patients (48.83%) have LN. involvement and the other patient (51.16%) haven't LN. involvement and didn’t get benefit from L.N. dissection.

Table (2): Comparison between patients with and without L.N. involvement according to the clinical picture and radiology of the tumor.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lymph node involvement</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (N=47)</td>
<td>Yes (N=22)</td>
</tr>
<tr>
<td><strong>Clinical picture:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>–Ve L.N.</td>
<td>38 (80.85%)</td>
<td>3 (13.64%)</td>
</tr>
<tr>
<td>+Ve L.N.</td>
<td>9 (19.15%)</td>
<td>19 (86.36%)</td>
</tr>
<tr>
<td><strong>Radiology:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>–Ve L.N.</td>
<td>40 (85.11%)</td>
<td>7 (14.89%)</td>
</tr>
<tr>
<td>+Ve L.N.</td>
<td>7 (14.89%)</td>
<td>19 (86.36%)</td>
</tr>
</tbody>
</table>

Table (3): Comparison between sensitivity of clinical and radiological examination in detection of L.N. involvement.

<table>
<thead>
<tr>
<th>Clinically detected L.N.</th>
<th>U/S detected L.N.</th>
<th>Real L.N. involvement</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>17</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>+</td>
<td>–</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td>35</td>
</tr>
<tr>
<td>–</td>
<td>+</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td>–</td>
<td>+</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>+</td>
<td>3</td>
</tr>
<tr>
<td>+</td>
<td>–</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>69</td>
</tr>
</tbody>
</table>

All Factor affecting LN involvement are listed in (Table 4).

Table (4): All factor affecting LN involvement.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
<th>Odds ratio (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females vs. males</td>
<td>0.72 (0.22-2.32)</td>
<td>0.58</td>
<td>1.027 (0.12-8.87)</td>
<td>0.98</td>
</tr>
<tr>
<td>Age &gt;50 vs. age &lt;50</td>
<td>3.5 (1.21-10.15)</td>
<td>0.02</td>
<td>3.69 (0.34-40.26)</td>
<td>0.28</td>
</tr>
<tr>
<td>Follicular variant vs. papillary</td>
<td>0.64 (0.17-2.33)</td>
<td>0.50</td>
<td>3.35 (0.16-71.06)</td>
<td>0.44</td>
</tr>
<tr>
<td>Follicular vs. papillary</td>
<td>0.44 (0.08-2.32)</td>
<td>0.33</td>
<td>1.88 (0.06-57.54)</td>
<td>0.72</td>
</tr>
<tr>
<td>Size &gt;2 vs. size &lt;2</td>
<td>0.72 (0.25-2.09)</td>
<td>0.55</td>
<td>0.15 (0.01-2.59)</td>
<td>0.19</td>
</tr>
<tr>
<td>Capsular invasion vs. none</td>
<td>2.44 (0.80-7.47)</td>
<td>0.12</td>
<td>5.48 (0.32-92.62)</td>
<td>0.24</td>
</tr>
<tr>
<td>Multifocality vs. none</td>
<td>2.82 (0.88-9.10)</td>
<td>0.08</td>
<td>1.33 (0.12-14.92)</td>
<td>0.82</td>
</tr>
<tr>
<td>Obviously clinically detectable vs. not</td>
<td>26.74 (6.48-110.40)</td>
<td>&lt;0.0001</td>
<td>13.02 (1.47-115.11)</td>
<td>0.02</td>
</tr>
<tr>
<td>Obviously radiological detectable vs. not</td>
<td>36.19 (8.42-155.61)</td>
<td>&lt;0.0001</td>
<td>11.95 (1.31-109.36)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CI: Confidence Interval.

p-value obtained from logistic regression.

*: Adjusted to other factors in the table.

Odds ratio of follicular vs. papillary=0.49 (0.09-2.51), p=0.39.
• By comparison between those with L.N. involvement according to age and sex:
  
  There is no increase in risk of lateral L.N. involvement with increasing age, or sex of the patient.

• By comparison between those with or without L.N. involvement according to pathological characteristics of tumors as pathological type, size, and multifocality: There is no significant difference and the result is not satisfactory due to low number of cases while invasion of thyroid capsule was associated with increased risk of lateral LN involvement. By comparison between those with and without L.N. involvement according to clinical picture and radiology of the tumor there is significant difference with \( p \)-value <0.0001 (Table 3).

• 19 cases of the 22 cases that have L.N. involvement (86.36%) were detected clinically with sensitivity of 86.36%, and positive predictive value of 67.86%.

And 38 case of the 47 cases who don’t have L.N. involvement (80.85%) where confirmed clinically with specificity of 80.85%, and negative predictive value of 92.68%. Overall accuracy of clinical examination is 82.6%.

Of the 3 cases which weren’t detected by clinical examination, 2 were detected by neck U/S examination and 1 was not detected by either of them.

• On the other hand 19 cases of the 22 cases that have L.N. involvement were confirmed radiologically by neck U/S with Sensitivity of 86.36%, and positive predictive value of 73.08%.

And 40 cases of the 47 cases that don't have L.N. involvement were confirmed radiologically with specificity of 86.36%, and negative predictive value of 93.02%.

Overall accuracy of neck U/S is 85.5%.

And of the 3 case which weren't detected by neck U/S, 2 were detected by clinical examination and 1 was not detected by either of them.

• If we use both neck U/S and clinical examination so as we consider that the test is positive, if clinical examination and/or neck U/S is positive: 21 cases of the 22 cases that have L.N. involvement were detected with sensitivity of 95.45%, and positive predictive value of 63.64%.

And 35 cases of the 47 cases that don't have L.N. involvement where confirmed by both the clinical and theradiological examination with specificity of 74.47%, and negative predictive value of 97.22%.

• By adjusting all the factors to each other: The most important factors for detecting L.N. involvement are the clinical picture and the radiological appearance on Neck U/S, with \( p \)-value of (0.008) and (0.001) respectively (Table 5).

**Discussion**

Treated differentiated thyroid cancer is generally has excellent prognosis, with 10-year overall survival rates exceeding 90% [14-16]. Total thyroidectomy is generally accepted as the procedure of choice for all papillary thyroid carcinomas exceeding 10mm in diameter [14,15].

Regional lymph node involvement is associated with increased tumor recurrence [14,17], and recurrence rates are higher in node positive patients over the age of 45 years [17]. Routine prophylactic central node dissection is not recommended by Western guidelines [18-20]. In contrast, the Japanese guideline recommends routine prophylactic node dissection of central LN [2]. This is because, centralnode metastasis is difficult to be evaluated preoperatively, andsecond operation for recurrence to this compartment may cause severe complications such as persistent hypoparathyroidism and recurrent laryngeal nerve injury. For patients showing clinical lateral node metastasis (N1b), it is mandatory to perform therapeutic lateral node dissection. Clinical lateral node metastasis is an important and independent prognostic factor [22,23]. Especially, patients having metastatic nodes larger than 3cm or extranodal tumorextension have a significantly worse disease-free survival [24].

Result from this study showed that clinical examination and Neck U/S were independent predictors of lymph node metastasis.

It's important whether or not tumor size is predictor of lymph node metastasis. Some studies have showed that L.N. metastasis is associated with large tumor size as shown by Kasiand Sakamoto [13], Kim By et al., [25] and Deplan D. et al., [26]. However, our study and other studies by So
et al., [28] and Roh et al., [29] reported that tumor size was an independent predictor of lymph node metastasis in multivariate analysis.

In the present study there is no relation between age and L.N. metastasis in consistence with other earlier studies [27]. Previous studies found inconsistent results regarding the association between gender and lymph node metastasis. In our study and Roh et al., [29] reported that there was no association between gender and lymph node metastasis.

Mazzaferri [30] and Ryan et al., [31] reported that there is increased risk of lymph node involvement in papillary thyroid cancer more than follicular thyroid cancer. But in our research we found no relation between tumor pathological type and lateral lymph node metastasis. This may be due to low number of cases in our study.

We found no relation between tumor multifocality and lymph Node metastasis. But in the study by Hay et al., [32] multifocality increase the risk of lateral lymph nodal recurrence with 11% of multifocal tumors exhibiting recurrence compared with only 4% of unifocal tumors.

And on the other hand Roh et al., [29] reported that there was no relation between tumor multifocality and lymph Node metastasis.

In this study capsular invasion is associated with increased risk of lateral lymph node involvement which is parallel to other studies which states that tumor extension beyond the thyroid capsule is generally associated with poor prognosis and large studies have demonstrated via multivariate analysis that it represents an adverse prognostic factor [33,34]. But Moon et al., [35] showed that minimal extrathyroidal extension was significantly associated with lymph node metastasis.

In both PTC and FTC, histological detected vascular invasion of the tumor is a sign of tumor aggressiveness, leading to hemotogenous invasion, distant metastases, and consequent poorer prognosis [36]. It has been demonstrated that DTC tumors with intra-and/or extra-thyroidal vascular invasion are prone to local recurrences and distant metastases, more frequent in FTC [37].

Diagnostic accuracy for lateral node metastasis on ultrasonography is somewhat better than that for central node metastasis, but the negative predictive value and sensitivity remain low at 43% and 29%, respectively. Furthermore, the incidence of lateral node metastasis for cases that are not preoperatively diagnosed as negative increases with tumor size, and about 75% of patients with primary lesions larger than 2cm demonstrated latent metastasis in this compartment [38].

And as shown in this study there is a strong association of lymph node with reported positive lymph node detected by clinical examination and neck U/S.

Clinical examination has sensitivity of (86.36%), specificity of (80.85%), positive predictive value of 67.86% and negative predictive value of 92.68%. Neck U/S examination has sensitivity of (86.36%) and specificity of (85.11%), positive predictive value of 73.08% and negative predictive value of 93.02%. By combining both neck U/S and clinical examination so as we consider that the test is positive, if clinical examination and/or neck U/S is positive. They will have sensitivity of (95.45%) and specificity of (74.47%), positive predictive value of 63.64% and negative predictive value of 97.22%.

So they both are the only reliable and effective factors to be used as predictor of lateral lymph node involvement and so, indicated lateral lymph node dissection.

This study has several limitations that must be kept in mind. First, since this study was retrospective analysis, the prognostic significance of lymph node metastasis such as the relation to tumor recurrence has not fully investigated. The long-term studies are needed to confirm the prognostic significance of lymph node metastasis. Second, our study population was a cohort of patient carried for a single center. Therefore, it is unlikely that this cohort of small provides reliable statements, and a much larger number of subjects in multicenter will be needed to generalize these results.

Conclusion:

After analysis of clinicopathologic factors which may affect lymph node involvement in well differentiated thyroid cancer, we found that the most dependent and reliable factors to detect lymph node involvement in the positive clinical examination and U/S neck examination, which indicate lymph node dissection. They together have sensitivity of 95.45% and specificity of 74.47%. According to the good prognosis of well differentiated thyroid cancer and the unproven benefit of prophylactic lateral lymph node dissection, make these two factors enough and efficient in detecting lateral lymph node in well differentiated thyroid cancer.
References


