

Identifying Risk Factors for a High Lymph Node Ratio (over 0.8) in Papillary Thyroid Carcinoma Patients

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Research

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Abstract

Background Despite the majority of papillary thyroid carcinoma (PTC) patients has an excellent prognosis, central lymph node metastases (CLNM) are common. The relationship between CLNM and prognosis is still controversial, however, a certain lymph node ratio (LNR) has been reported to show significantly worse prognosis for PTC patients. Therefore, the extent of CLNM seems to play an important role in predicting the recurrence and survival of PTC. The aim of this study is to determine the risk factors for a high LNR (over 0.8) in central compartment in PTC patients.

Methods A retrospective cohort study was conducted on PTC patients who underwent total thyroidectomy or lobectomy plus central lymph node dissection (CLND) between January 2011 and December 2015. Patients with an LNR over 0.8 was defined as Group A, and patients with an LNR 0 was defined as group B. The clinical and pathological factors such as gender, age, tumor size, tumor number, extracapsular spread (ECS), MACIS score, and co-existence of chronic lymphocytic thyroiditis [CLT] were compared between different LNR groups.

Results Univariate analysis found high LNR to be associated with male gender, young age (<40 years), larger tumor (≥ 1 cm), ECS and absence of chronic lymphocytic thyroiditis. Multivariate logistic regression showed male gender ($p = 0.007$, OR = 3.79), young age (<40 years) ($p = 0.000$, OR = 0.159), larger tumor (≥ 1 cm) ($p = 0.033$, OR = 2.530), and absence of chronic lymphocytic thyroiditis ($p = 0.036$, OR = 0.321) to be independent predictors for high LNR in PTC patients

Conclusions Male gender, younger age (<40 years), larger tumor (≥ 1 cm) and absence of chronic lymphocytic thyroiditis were risk factors of high LNR. We recommend a prophylactic CLND should be considered in PTC patients with such risk factors.

Introduction

The incidence of thyroid cancer has been increasing worldwide during the past two decades. Among these patients, papillary thyroid cancer (PTC) accounts for the most widespread histological type. Although it has been generally accepted that the majority of PTC patients has an excellent prognosis, central lymph node metastases (CLNM) are common when diagnosed. However, prophylactic central lymph node dissection (CLND) in the treatment of cN0 PTC is still controversial.¹ LNM has been reported to be related with increased local recurrence rates² and reduced survival³, and the extent of CLNM seems to play an important role in predicting the prognosis for PTC. Several studies have highlighted that a certain LNR could be an independent predictor for the recurrence for PTC.⁴⁻⁶ The risk factors for LNR has been studied before, however, the risk factors for a high LNR (over 0.8) in central compartment has not yet been investigated. The aim of this study is to determine the risk factors for a high LNR (over 0.8) in central compartment for PTC. The outcome of the study could assist in making a more appropriate selection of patients for prophylactic CLND.

Patients And Methods

This retrospective cohort study was performed of a single institutional database of patients with histologically proven PTC at Peking Union Medical College Hospital from January 2011 to December 2015. All patients underwent pre-operative examination by US to evaluate the size of tumor and the presence of CLNM. All patients were diagnosed with PTC pre-operatively by fine-needle aspiration biopsy or intra-operatively on frozen section. Inclusion criteria were as follows: patients who underwent total thyroidectomy or lobectomy plus prophylactic CLND with or without lateral neck dissection, patients with LNR>0.8 or LNR=0 in central compartment. Of the 5925 patients treated surgically for PTC from January 2011 to December 2015, 210 patients satisfied inclusion criteria.

Patients were divided into two groups according to LNR value in central compartment. Patients with LNR>0.8 were defined as Group A, and patients with LNR=0 were defined as Group B. The clinical and pathological factors such as gender, age, tumor size, tumor number, extracapsular spread (ECS), MACIS score and coexistence of CLT were compared between different groups.

Statistical analysis was performed using SPSS17.0 software. Data were compared for statistical analysis, using the Student's t test to compare quantitative variables and using the chi-square tests to evaluate differences between qualitative variables, multivariate logistic regression analysis was performed to identify the multivariate correlates of a high LNR, $P < 0.05$ was considered significant.

Results

210 patients were included in this study. Patient characteristics are summarized and the relationship between LNR value and clinical factors were analyzed between group A and group B based on operative and surgical pathology reports in Table 1. Male gender, young age (< 40 years), larger tumor (≥ 1 cm), coexistence of chronic lymphocytic thyroiditis and ECS were significantly related to high LNR in central compartment ($P < 0.05$). There were no significant differences in the tumor number, MACIS score, and other tumor pathologic characteristics. A multivariate analysis was performed to determine whether these parameters were independently correlated with high LNR in central compartment. Male gender, young age (< 40 years), larger tumor (≥ 1 cm), absence of chronic lymphocytic thyroiditis turned out to be independently predictive factors for high LNR in central compartment. (Table 1). The median number of lymph nodes excised was 8.9 in group A and 11.0 in group B ($P > 0.05$).

Discussion

Although it has been accepted that patients with PTC have a favorable prognosis⁷, cervical LNM are common, with an incidence between 30% and 80%. Liu FH and Grant CS reported that the risk of recurrence ranges from 5–21% in PTC patients with cervical LNM.^{8,9} However, there were other studies showed that cervical LNM did not affect recurrence and survival. The extent of cervical LNM seems to play an important role in predicting the prognosis of PTC. For example, several reports identified that LNR

(the number of metastatic LN divided by the number of harvested LN) appears to predict the rate of recurrence in PTC.^{10,11} A certain LNR has been reported to show significantly worse prognosis for PTC patients. Schneider, et al⁶ showed that PTC patients with a total LNR over 0.7 or LNR over 0.86 in central compartment had significantly worse disease-free survival rates. However, there were few studies on the risk factors for LNR, and even less for a high LNR. The aim of this study is to determine the risk factors for a high LNR (over 0.8) in central compartment for PTC patients.

It is generally agreed that the LNR is affected by the patient's individual clinicopathologic characteristics in malignancies such as gender, age, tumor size, multifocality, extra-thyroid invasion and so on. It would be beneficial to identify the subset of patients with PTC who have aggressive pathological features so that a full treatment protocol could be provided.

The present study revealed that male gender, younger age (< 40 years), larger tumor (≥ 1 cm) and co-existence of chronic lymphocytic thyroiditis were independent risk factors for high LNR.

Although women have been shown to be more susceptible to PTC than men, male gender has been suggested as an important risk factor for LNM in previous reports^{12,13}. Our previous study also showed male sex was an independent indicator for LNM in papillary thyroid microcarcinoma. In this study, male gender had 3.79 times higher risk of high LNR than female.

Although age is a significant factor in PTC staging systems and old age correlates with a poor prognosis, young age was found to be an independent risk factor for high LNR in present study. The relationship between age and LNM rates has been studied before. Jing Wang et al¹⁴ analyzed a total of 46,077 PTC patients from the SEER database, and identified that in each T stage, LNM rates were inversely associated with age at diagnosis, which was validated by multivariate logistic regression analysis ($p < 0.001$). In addition, the study also showed that the subset of patients 30 or younger had the highest LNR compared with other subsets ($p < 0.001$). Our study also showed younger age (< 40 years) is a predictive risk factor for high LNR.

Several studies had revealed that lymph node metastasis increased with the increase in tumor size, and larger tumor size was an independent predictor for CLNM.¹⁵⁻¹⁷ Our research showed that tumor size ≥ 1 cm was independently predictive of high LNR in CLNM.

Zeng et al¹⁸ found that coexisting chronic lymphocytic thyroiditis (CLT) was an independent predictive factor for LLNM. Conversely, a meta-analysis by Lee et al¹⁹ suggested that PTCs with coexisting CLT had a significant negative association with LNM (odds ratio [OR] 1.3, $P = .041$); Borowczyk M et al²⁰ reported that CLT plays a protective role in preventing the spread of the differential thyroid cancer. In his study, in CLT group, the prevalence of pT1 was greater than for pT2-pT4 DTC ($P = 0.0003$; OR = 1.69, 95% CI 1.27–2.24) compared to controls (68.3 vs. 56.1%, respectively). The thyroid capsule infiltration without extrathyroidal invasion ($P < 0.0001$; OR = 0.21, 95% CI 0.14–0.31) was more frequent in CLT group, unlike extracapsular invasion, which was significantly more often present in patients with DTC but without CLT

($P = 0.004$; OR = 1.66; 95% CI 1.17–2.34) as well as nodal involvement ($P = 0.048$; OR = 0.65, 95% CI 0.42–0.99). Myshunina TM²¹ also found that the presence of CLT in papillary carcinoma patients showed a certain positive impact on the course of the disease, in particular, primary tumor growth, invasion, and metastasis. To further investigate the mechanism, Pilli T et al²² demonstrated that CLT has a positive prognostic value in PTC patients, and the imbalance between cytotoxic and regulatory T lymphocytes in the peri-tumoral without the background of CLT may affect the tumor-specific immune response favoring a more aggressive behavior of cancer. Lubin D²³ demonstrated that PTC arising in a background of CLT shows increased PD-L1 (programmed death-ligand 1) expression, which is retained with metastasis. The results of present study showed that PTC patients with coexisting CLT had a negative association with high LNR.

This study has several potential limitations. First, this was a retrospective study and conducted in a single institution. Furthermore, Some clinicopathologic risk factors such as histological subtype,

BRAF gene mutation were not provided because they were not routinely reported in the pathological report. Finally, the number of cases enrolled is still not large enough.

In conclusion, a high LNR may be predicted by clinical features such as male gender, young age and co-existence of CLT. Our findings may help to guide clinicians in the selection of candidates suitable for Prophylactic CLND.

Declarations

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Author Contributions

Yuewu liu planned the study and performed quality evaluation. Liyang zhang extracted data and wrote the manuscript. Xiaoyi li and Hongfeng liu resolved any disputes. All authors screened and approved the

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, table 1 and table 2 are only available as a download in the Supplemental Files section.

Supplementary Files

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