The Clinical and Prognosis Value of the Number of Metastatic Lymph Nodes in Papillary Thyroid Carcinoma Patients

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Research

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Abstract

Objective: It has been reported that papillary thyroid carcinoma (PTC) patients with lymph node metastasis (LNM) are more associated with adverse outcomes. This study aimed to assess the correlation between the lymph node (LN) status and clinical prognosis in PTC patients.

Methods: We retrospectively reviewed the medical records of PTC patients who underwent initial thyroid cancer surgery in Renmin Hospital of Wuhan University between 2017 and 2019. 1021 PTC patients with total checked number of lymph nodes ≥ 5 were involved in this study. The clinicopathological characteristics of patients were compared according to the LN status and the number of metastatic lymph nodes (NMLNs).

Results: The LNM and NMLNs >5 were seen in 694 (68.0%) and 222 (21.7%) cases, respectively. Young patients, patients with larger tumor diameter, bilaterality, multifocality and gross extrathyroidal extension (ETE) were more inclined to LNM and NMLNs >5 ($P < 0.001$). The patients with LNM (pN1) were mainly among males and were exhibited multifocality and advanced tumor stage ($P < 0.001$), while pN1 patients with NMLNs >5 were negatively associated with advanced tumour stage ($P < 0.05$). Recurrence-free survival among pN1 patients was significantly different between 2 groups (NMLNs ≤ 5 : 0/472, 100.0%; NMLNs >5 : 5/222, 97.7%; $P = 0.002$). In multivariate logistic regression analysis, the male (OR=2.580, $P < 0.001$), 10-mm tumor size (OR=1.770, $P < 0.001$), tumor gross ETE (OR=2.004, $P < 0.001$) were independent predictors for the high prevalence of LNM. Similarly, 10-mm tumor size (OR=1.399, $P < 0.05$), bilaterality (OR=2.350, $P < 0.001$) and tumor gross ETE (OR=2.660, $P < 0.05$) were also independent predictors for the high prevalence of NMLNs >5 ; 10-year age was an independent predictor for the low prevalence of the LNM (OR=0.658, $P < 0.001$) and NMLNs >5 (OR=0.678, $P < 0.001$).

Conclusions: The status of the cervical LNs and the NMLNs should be correctly evaluated to guide reasonable treatment and careful follow-up.

Background

Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma (TC) with a low rate of mortality even in advanced stages, and an excellent 10-year overall survival [1]. However, the incidence and recurrence rate of PTC is gradually increasing throughout the world [2, 3]. Several works of literature have reported the involvement of central cervical lymph node metastasis (CLNM) and lateral cervical lymph node metastasis (LLNM) with PTC patients, and 80% of long-term recurrence cases have locoregional cervical lymph nodes metastasis (LNM)(pN1) [4-6]. In addition, several studies have reported that LNM is a reliable predictor of recurrence [7, 8] and poor prognosis [5, 9]. However, many researchers [7, 10] conducted meta-analyses on the risk factors of LNM and found that the risk factors of LNM in PTC patients were inconsistent across different studies. In recent years, more researcher attention is being applied to the features of metastatic lymph nodes (LNs), such as the location of metastatic LNs, the number of metastatic lymph nodes (NMLNs), and the maximum diameter of the metastatic LNs and the

metastatic LN ratio (mLNR). On the one hand, many scholars have tried to establish a standard for recurrence risk stratification of PTC patients according to the characteristics of metastasis LNs. They found that the risk of recurrence was higher among PTC patients with larger metastatic LNs or higher mLNR [11-14]. As declared in the most recent American Thyroid Association (ATA) risk stratification system, the recurrence rate of pN1 PTC with ≤ 5 LNs involved or >5 LNs involved is 5% and 20%, respectively [1]. Nevertheless, in the AJCC TNM staging system [15], postoperative LN involvement was only divided into CLNM alone (pN1a) and LLNM (pN1b). Thus, many scholars suggested that adding the features of metastatic LNs into the current American Joint Committee on Cancer (AJCC) staging system [12, 14]. On the other hand, some investigators tried to analyze the clinical response of PTC patients with different characteristics of metastatic LNs. Gao et al. [16] found that excellent therapeutic effect was mainly among patients with lower mLNR and NMLNs. Determination of high-risk patients and the administration of appropriate treatment are essential in the clinical treatment and management of PTC. Because there is no requirement for a minimum number of lymph nodes to be sampled, the clinical management of cervical LNs for PTC patients is still controversial [14]. This retrospective study explored the relationship between the features of LNM and NMLNs and outcome in PTC patients, and aimed to provide substantial evidence in the medical practice of PTC.

Patients And Methods

Patients selection

The data of 2424 TC patients who underwent surgery for thyroid cancer from 2017 to 2019 at the Department of Breast and Thyroid Surgery of the Renmin Hospital of Wuhan University (Wuhan, Hubei, the People's Republic of China) were retrospectively collected. The process of selecting qualified patients for analysis are shown in **Fig. 1**. Patients who had follicular, medullary, or anaplastic thyroid carcinoma, or underwent a second operation, or had recurrence disease, or had incomplete medical records were excluded. It should be emphasized that the surgical treatment of LNs in PTC patients among different hospitals is still different and is more depending on the surgeon's judgment of procedural safety [4, 17]. There were great differences in cervical LNM of PTC patients in our hospital and there was no unified standard for the number of LNs dissections per patient. A quite few [12-14] articles found that a greater NMLNs might be associated with lower survival. Similarly, patients with NMLNs ≥ 5 were divided into intermediate risk in the improved risk stratification of recent ATA guideline [1]. Unfortunately, the number of LNs sampled and the NMLNs are no relevant cut-off value till now. Our current study aim to testify the clinical and prognosis significance of NMLNs ≥ 5 among pN1 patients. In this study, we excluded patients who didn't underwent prophylactic ipsilateral central cervical LN dissection (CLND) and therapeutic and modified radical lateral neck dissection (MND). According to total number of LNs checked, we retrieved data for 1021 eligible PTC patients who had total checked number of LNs ≥ 5 so as to reduce difference of LNs dissections. We categorized the subjects into two groups according to the LN stage and comparatively analyzed. Then, the clinicopathological characteristics of pN1 patients was further compared based on NMLNs. The follow-up time was from the operation date to the recurrence or the last

follow-up months or July 1st, 2020. Institutional Ethics Review Committee of the Renmin Hospital of Wuhan University approved the study (2042019kf0229). All patients signed written informed consent.

Surgical treatment

Patients underwent lobectomy or total thyroidectomy (includes isthmus) based on the criteria outlined in the 2015 ATA manual, with prophylactic ipsilateral CLND as a standard procedure for TC patients at the hospital. For patients with a sign of LLNM in preoperative cervical ultrasonography (US) and then confirmed as LLNM by fine needle aspiration pathology, MND was simultaneously performed [1]. The CLND extends superiorly to the hyoid bone, inferiorly to the innominate vein, laterally to the carotid sheath, and dorsally to the prevertebral fascia. The improved MND is defined as the complete removal of level I to level IV lateral neck LNs. If there was no evidence for metastasis, levels I and II dissections were not be performed.

Pathological examination

All the subjects were routinely examined preoperatively through cervical US and postoperatively through pathological examination. Pathological findings were obtained from the Department of Pathology, Renmin Hospital of Wuhan University. The report evaluated the maximum diameter of the primary tumor, unilaterality or bilaterality, number of lesions, the presence or absence of ETE, the location of metastatic LNs and the NMLNs, tumor node metastasis (TNM) staging, BRAF status, and the presence of Hashimoto's thyroiditis (HT).

We defined multifocality as the presence of two or more tumor foci of PTC regardless of unilaterality or bilaterality. According to the degree of invasion, histological ETE was divided into ETE and no ETE. Based on postoperative pathology, regional metastatic LNs can be divided into no cervical LNM (pN0), CLNM alone (pN1a), and LLNM (pN1b). We focused on the characteristics of metastatic LNs, including the location and the NMLNs. Pathological staging of tumors was adopted from the eighth edition of AJCC TNM staging system [15], which shows no difference based on the difference between pN1a and pN1b. The BRAF^{V600E} mutation test was performed only in 128 cases.

Statistical analysis

The data were analyzed by SPSS 25.0 software program (IBM Corp., Armonk, NY, USA). The continuous variables were described by mean $\pm$ standard deviation ($M \pm SD$) and median. The significant difference between groups was analyzed using Student's *t*-test or the rank test. The classified variables were expressed as the number of cases in percentage. The chi-square test or Fisher's exact test was used for categorical variables. Log rank tests and Kaplan Meier method were employed to compare the recurrence free survival (RFS). Univariate logistic regression analysis was used to calculate odds ratios (ORs) as well as the 95% confidence intervals (CIs) for LNM and NMLNs >5 . Variables with a *P*-value <0.05 were included in the multivariate logistic regression analysis to determine the association between

clinicopathological characteristics and LNM, NMLNs >5. All tests were two sided and P -value <0.05 was indicated statistical significance.

Results

Baseline clinicopathological characteristics of PTC patients

The baseline clinicopathological characteristics of 1021 PTC patients are shown in **Table 1**. With a median age of 45 years old and a median primary tumor size of 9.0 mm, the ratio of females and males of all eligible patients was 75.8% and 24.2%. 563 (55.1%) patients were diagnosed as papillary thyroid microcarcinoma (PTMC) by pathology. pN0 and pN1 were separately found in 327 (32.0%) and 694 (68.0%) cases, respectively. Further analysis showed that NMLNs ≤ 5 and NMLNs >5 were seen in 799 (78.3%) and 222 (21.7%) cases. Bilaterality, multifocality and ETE was confirmed in 32.4%, 40.3%, 74.8% of patients. The proportion of TNM stage I and TNM stage II was 89.0% and 11.0%. There were 103 and 158 cases of BRAF^{-V600E} mutation and HT respectively. The median time interval follow-up was 22 months (range 4–42 months).

Clinicopathological characteristics of PTC patients based on LN stage

The clinicopathological characteristics of PTC patients based on the LN stage are shown in **Table 2**. Among 1021 pathologically proven PTC patients, 694 (68.0%) harbored LNM (pN1). Compared with pN0 patients, pN1 patients were significantly younger (42.1 years vs 48.3 years, $P < 0.001$), mainly among males (29.1% vs 13.8%, $P < 0.001$) and with larger tumor size (13.2 mm vs 8.5 mm, $P < 0.001$). Further analysis showed that non-PTMC patients were susceptible to LNM compared with PTMC patients (53.6% vs 26.3%, $P < 0.001$). Moreover, bilaterality (36.3% vs 24.3%, $P < 0.001$), multiplicity (43.9% vs 32.4%, $P < 0.001$), ETE (81.4% vs 60.9%, $P < 0.001$) and advanced TNM stage (15.6% vs 1.2%, $P < 0.001$) were significantly frequent in pN1 patients. The HT or BRAF^{-V600E} mutation were not associated with the LN stage.

Clinicopathological characteristics of pN1 patients based on NMLNs

According to 2015 (ATA) guidelines, pN1 PTC with ≤ 5 LNs involved or > 5 LNs involved had different recurrence risk. To verify the clinical significance of NMLNs among pN1 patients, a comparison of clinicopathological characteristics of pN1 patients was based on NMLNs ≤ 5 or >5. As shown in **Table 3**, in all patients, NMLNs ≤ 5 and NMLNs >5 were evident in 472 (68.0%) and 222 (32.0%), respectively. Patients with NMLNs >5 were significantly younger compared to those with NMLNs ≤ 5 (38.8 years vs 43.7 years, $P < 0.001$). Although patients with NMLNs >5 were more common among the males, there was no statistical significance (33.3% vs 27.1%, $P = 0.093$). The NMLNs >5 was significantly associated with larger tumour diameter (16.4 mm vs 11.7 mm, $P < 0.001$), bilaterality (49.5% vs 30.1%, $P < 0.001$) and ETE (92.3% vs 76.3%, $P < 0.001$), compared with NMLNs ≤ 5 . Further analysis showed that non-PTMC patients were prone to NMLNs >5 compared to PTMC patients (66.9% vs 44.9%, $P < 0.001$). However, there was a negative correlation between the advanced TNM stage (11.3% vs 17.6%, $P < 0.05$) in NMLNs >5 compared

with NMLNs ≤ 5 . However, multiplicity, HT or a positive BRAF^{V600E} mutation was not associated with NMLNs.

Correlation between clinicopathological characteristics of PTC patients and LNM

The association between clinicopathological characteristics and LNM was analyzed in PTC patients. As depicted in **Table 4 and Fig. 2**, male gender (OR=2.580, $P<0.001$), 10-mm tumor size (OR=1.770, $P<0.001$), and tumor gross ETE (OR=2.004, $P<0.001$) were independent predictors for the high prevalence of LNM. However, 10-year age (OR=0.658, $P<0.001$) were independent predictors for the low prevalence of LNM.

Correlation between clinicopathological characteristics of pN1 patients and the NMLNs >5

The association between clinicopathological characteristics and the NMLNs >5 was analyzed in pN1 patients. As depicted in **Table 5 and Fig. 3**, 10-mm tumor size (OR=1.399, $P<0.05$), bilaterality (OR=2.350, $P<0.001$) and tumor gross ETE (OR=2.660, $P<0.05$) were independent predictors for high prevalence of NMLNs >5. However, 10-year age (OR=0.678, $P<0.001$) was an independent predictor for low prevalence of NMLNs >5.

Recurrence-free survival based on LN stage and NMLNs

During the median follow-up period of 22 months (range 4-42 months), five cases of disease recurrence were identified across all patients. LN stage didn't affect recurrence-free survival (RFS). (pN0: 0/327, 100.0%; pN1: 5/694, 99.3%; $P=0.104$; **Fig. 4**). However, RFS among pN1 patients was significantly different between 2 groups (NMLNs ≤ 5 : 0/472, 100.0%; NMLNs >5: 5/222, 97.7%; $P=0.002$; **Fig. 5**).

Discussion

Although a good prognostic value of PTC was reported, recurrence, metastasis, and death among PTC patients were also evident [2, 18]. PTC patients with LNM have a higher rate of recurrence and disease-specific mortality [7, 19]. Therefore, knowledge of the characteristic of patients with LNM and the predictors for LNM in PTC patient is highly required. The purpose of this study was to evaluate the influence of the location of metastatic LNs and NMLNs on prognosis of PTC patients. We found a significant correlation between several prognostic variables and LNM and NMLNs >5. Patients with LNM and a greater NMLNs were related to aggressive characteristics, such as a larger primary tumor size, the presence of grossly ETE. We also found RFS was a significantly difference between PTC patients with NMLNs ≤ 5 and PTC patients with NMLNs >5.

Old age is a risk factor for poor prognosis of PTC patients [15, 20] and a recent AJCC TNM staging system used a 55-years cutoff to upstage patients. Whereas Jeon et al. [21] reported that patients aged ≥ 45 years were at a higher risk of LNM; other studies revealed that young people are also more likely to have LNM [22]. Our data revealed that patients aged <55 years were more prone to LNM and NMLNs >5 and ten-year age was an independent predictor for the low prevalence of LNM and NMLNs >5. However,

Spinelli et al. [23] retrospectively discussed the clinical characteristics of 132 children and adolescents with PTC and found that age was not related to LNM. These results vary from ours due to difference in the target population. In this study, however, we sampled PTC patients of all ages, which could provide reliable evidence that LNM and NMLNs >5 were frequent in young patients. Prophylactic CLND should be recommended during thyroidectomy for patients younger than 55 years old. Nevertheless, prophylactic CLND may lead complications that could significantly influence the quality of life [1]. Therefore, a balance between the risks and benefits of prophylactic CLND deserves further discussion. The association between gender with LNM is controversial. Results and findings from similar studies are inconsistent. In many studies, the association between male and CLNM were significant [22]. However, Spinelli et al. [23] reported no significant correlation. In our study, ratio of female /male ratio was 1:3, which was consistent with previous studies [2]. We found that male patients were susceptible to LNM but also an independent predictor for the high prevalence LNM. However, no relationship was observed between male patients and NMLNs >5. Our results were similar but not identical to the finding reported by Sheng et al. [22], who found that male predict increased a high number of CLNM ($n \geq 5$) in PTMC patients.

We detected a characteristic relationship between metastatic LNs and the original PTC lesion. PTMC, with a diameter ≤ 10 mm, has a better prognosis than PTC [1]. Although investigators alarmed that PTMC might occur in LNM before diagnosis [24], pathological data from patients in our study confirmed that non-PTMC was more inclined to LNM and NMLNs >5. This could imply that patients with PTMC were low-risk. In addition, besides surgery, active surveillance could be an alternative approach for PTMC patients [1]. The tumor diameter of above 20 mm indicates the aggressiveness of PTC [1]. However, the effect of the tumor size on LNM in PTC varies greatly among different studies [24, 25]. In the present study, patients with a largely tumor diameter were prone to LNM and NMLNs >5. Furthermore, tumor size per 10mm was an independent risk factor for LNM and NMLNs >5. Hence, a larger tumor size could be a risk factor for worse LN status, which should be more concerned by clinicians. Several studies have concluded that patients with LNM are likely associated with bilateral cancer and multifocality [9, 26], but the correlation between bilaterality and multifocality and NMLNs have been rarely conducted. And the impact of these two factors on metastatic LNs remains controversial [22]. We found that LNM and NMLNs >5 were associated with bilaterality. Whereas bilaterality was a high-risk factor for NMLNs >5, multifocality wasn't a high-risk factor for neither LNM nor NMLNs >5. The determination of the correlation between LN status and ETE is also critical. In our study, LNM and NMLNs >5 was associated with ETE, which was similar to previous reports [9, 27]. Furthermore, tumor gross ETE was the risk factor for the high prevalence LNM and NMLNs >5. Previous evidence showed that ETE had a severe influence on the prognosis of patients and high prevalence in the aggressive types of thyroid carcinoma, which cannot be overlooked [15, 28]. Li et al. [28] stated that the risk of LN involvement in patients without ETE was similar to that of patients with ETE into perithyroidal tissue but lower than those with T3b and ETE invading beyond the strap muscles. Unfortunately, we did not study the relationship between LNM and different extent of ETE.

Numerous works of literature reported an association of HT with less CLNM [9, 22, 29]. In this study, coexisting HT was not associated with LNM and NMLNs >5, which was found only in 158 patients, hence the results were not sufficient for a substantive conclusion. The presence of BRAF^{-V600E} mutation, common in PTC, causing change of valine-to-glutamic acid, resulting in an activation of the BRAF protein kinase and the microtubule-associated protein (MAP) kinase pathway, plays an important role in the progression and aggressiveness of PTC [30]. A previous study proposed a correlation between LN status and BRAF cytology [31]. Our data demonstrated BRAF^{-V600E} mutation was not apparently relevant to LNM and NMLNs >5 in PTC patients. Sheng et al. [22] and Zhang et al. [32] also noted that BRAF^{-V600E} mutation was not related to CLNM. But a rarely little research has been performed in this field regarding the relationship between BRAF^{-V600E} mutation and the NMLNs. The inconsistency in reporting the association between BRAF^{-V600E} mutation and LNM could be, to some extent, attributed to variation in mutation rates [31, 33, 34]. A BRAF^{-V600E} mutation was closely related to invasive long-term outcome, such as a higher disease-specific mortality and a shorter RFS [35, 36]. It is important to emphasize that patients with the identification of BRAF^{-V600E} mutation may need more aggressive treatment when there is the evidence of LNM, but not if there is no LNM [15]. Xing et.al [30] also pointed out that the application of the prognosis of mutations should be employed to meet the personalized needs of specific clinical conditions. If the NMLNs will affect treatment decisions of pN1 patient with a BRAF^{-V600E} mutation is also worthy of further discussion. Prospective studies with a large sample are needed to elucidate the relationship between BRAF^{-V600E} mutation and metastatic LNs to establish the appropriate operational strategy for patients with LNM.

As stated in previous studies, a larger size of metastatic LNs, or an increase in NMLNs, or a higher positive mLNR was associated with a higher risk of recurrence and reduced long-term survival [12, 13, 37, 38]. In the AJCC TNM staging system [15], postoperative LN involvement was only divided into pN1a and pN1b. Incorporating size of metastatic LNs, NMLNs and mLNR into the current AJCC staging system may improve the stratification of the risk groups [8, 12, 39]. However, the criteria for selecting the minimal number of examined LNs and the mLNR cut-off value have not been completely determined [6, 16, 17]. PTC patients with LNM were associated with advanced tumor stage. In contrast, pN1 patients with NMLNs >5 weren't associated with advanced tumor stage. Nevertheless, we emphasize an intense focus on NMLNs because 3-year RFS was significantly different between different NMLNs groups. Therefore, the features of metastatic LNs should be cautiously considered in the postoperative risk stratification even pN1 patients with low TNM staging.

Our research had several limitations. Firstly, it was inevitable to avoid the disadvantages of a single center and retrospective study. Secondly, we did not evaluate clinicopathological characteristics of patients with different sizes of metastatic LNs because of lack information on the size of metastatic LNs. Thirdly, the lack of data on 10-years follow-up of disease recurrence and survival prevented the evaluation of the relationship between LN status and recurrence and survival. Even so, this article is still worthy of reference, especially in the analysis of the characteristics of metastatic LNs in PTC patients. We enrolled a larger sample size and only retrieved PTC patients who had total checked number of LNs ≥ 5 so that

our data made difference to assessing the influence of LN status especially NMLNs on the clinicopathological characteristics of PTC patients. In the future, multiple-center and long-term prospective studies are proposed to clarify the correlation between LN status and various clinicopathological parameters in PTC patients and evaluate the influence of LNM on prognosis.

Overall, our findings suggested that LNM was frequent in patients with younger age, male gender, largely tumor diameter and tumor gross ETE. NMLNs >5 was more common in pN1 patients with younger age, largely tumor diameter, bilaterality and tumor gross ETE and more incline to have a reduced RFS. Certainly, sufficient clinical data and molecular biology theory to support this argument is required. To summarize, the information obtained from the clinicopathological risk factors, related to LNM and NMLNs>5, should be applied prognostically to guide subsequent treatment decisions, including the selective application of prophylactic CLND or additional treatment. Further studies on the characteristics of LNM will essential for prognostic judgment and decision-making in clinical practices to improve the health of patients.

Abbreviations

PTC: papillary thyroid carcinomas; LNs: lymph nodes; LNM: lymph node metastasis; CLND: central cervical lymph node dissection; MND: modified radical lateral neck dissection; NMLNs: number of metastatic lymph nodes; CLNM: central cervical lymph node metastasis; LLNM: lateral cervical lymph node metastasis; ETE: extrathyroidal extension; HT: Hashimoto's thyroiditis; ATA: American Thyroid Association; AJCC: American Joint Committee on Cancer.

Declarations

Author contributors: Ling Zhan and Hong-fang Feng performed the research and wrote the first draft. Ling Zhan, Hong-fang Feng, Jun-long Song, Xi-zi Yu, Ling-rui Li collected the data. Ling Zhan analyzed the data. All authors contributed to the design and interpretation of the study results, and reviewed and wrote the final paper.

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Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All participants in this research were diagnosed as papillary thyroid carcinomas at the Department of Breast and Thyroid Surgery, Renmin Hospital of Wuhan University, Wuhan, Hubei, P.R. China. The research was approved by the Ethical Review Committee of this hospital. Consent for publication Patients who participated in this research signed the informed consent and had complete clinical data.

Consent for publication

Patients who participated in this research signed the informed consent and had complete clinical data.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Tables

Table1 Baseline clinicopathological characteristics of PTC patients

Variates	Value
Cases of patients	1021
Age, median (range)	44.1±11.7, 45 (16-80)
Sex, male/female, number (%)	247/774 (24.2/75.8)
Primary tumor size, median (mm)	11.7±8.9, 9.0 (0.1-55.0)
PTMC/non-PTMC, number %	563/458 (55.1/44.9)
LN involvement, pN0/ pN1a/ pN1b, number (%)	327/520/174 (32.0/51.0/17.0)
NMLNs of patients, NMLNs ≤5/ NMLNs >5, number (%)	799/222 (78.3/21.7)
Bilaterality, number (%)	331 (32.4)
Multifocality, number (%)	411 (40.3)
ETE /without ETE, number (%)	764/257 (74.8/25.2)
TNM stage, I /II, number (%)	909/112 (89.0%/11.0%)
BRAF- ^{V600E} mutation, positive/negative/unknown, number (%)	103/25/893 (10.1/2.4/87.5)
HT, number (%)	158 (15.8)
Duration of follow up (months)	4-42 (22)

ETE: extrathyroidal extension; TNM stage: tumor node metastasis stage; HT: Hashimoto's thyroiditis;

Table 2 Clinicopathological characteristics of PTC patients based on LN stage

Clinicopathological characteristics	pN0 n=327	pN1 n=694	Total n=1021	P value
Age(years)				
M±S.D	48.3±10.8	42.1±11.7		<0.001*
<55	233/327(71.3)	585/694(84.3)	818	<0.001*
≥55	94/327(28.7)	109/694(15.7)	203	
Sex				
female	282/327 (86.2)	492/694 (70.9)	774	<0.001*
male	45/327 (13.8)	202/694 (29.1)	247	
Tumor size (mm)				
M±S.D	8.5±6.6	13.2±9.5		<0.001*
≤10mm	241/327(73.7)	322/694(46.4)	563	<0.001*
10-20mm	71/327(21.7)	274/694(39.5)	345	
20-40mm	13/327(4.0)	83/694(12.0)	96	
>40mm	2/327(0.6)	15/694(2.1)	17	
Bilaterality				
Present	79/327(24.2)	252/694(36.3)	331	<0.001*
Absent	248/327(75.8)	442/694(63.7)	690	
Multifocality				
Present	106/327(32.4)	305/694(43.9)	411	<0.001*
Absent	221/327(67.6)	389/694(56.1)	610	
ETE				
Present	199/327 (60.9)	565/694 (81.4)	764	<0.001*
Absent	128/327 (39.1)	129/694 (18.6)	257	
TNM Stage				
Ⅰ	323/327 (98.8)	586/694 (84.4)	909	<0.001*
Ⅱ	4/327 (1.2)	108/694 (15.6)	112	
HT				
Present	60/327 (18.3)	98/694 (14.1)	158	0.081

Absent	267/327 (81.7)	596/694 (85.9)	863	0.568
BRAF^{V600E}mutation				
Positive	35/42(83.3)	68/86 (79.1)	103	
Negative	7/42(16.7)	18/86(20.9)	25	

ETE: extrathyroidal extension; TNM stage: tumor node metastasis stage; HT: Hashimoto's thyroiditis; *: statistically significant difference.

Table 3 Clinicopathological characteristics of pN1 patients based on NMLNs

Clinicopathological characteristics	NMLNs ≤5 n=472	NMLNs >5 n=222	Total	P value	
Age (years)					
M±S.D	43.7±11.3	38.8±11.8		<0.001*	
<55	389/472 (82.4)	196/222(88.3)	585	0.047*	
≥55	83/472(17.6)	26/222(11.7)	109		
Sex					
female	344/472 (72.9)	148/222(66.7)	492	0.093	
male	128/472 (27.1)	74/222(33.3)	202		
Tumor size (mm)					
M±S.D	11.7±8.6	16.4±10.4		<0.001*	
≤10mm	260/472(55.1)	69/222(31.1)	329	<0.001*	
10-20mm	164/472(34.7)	103/222(46.4)	267		
20-40mm	40/472(8.5)	43/222(19.4)	83		
>40mm	8/472(1.7)	7/222(3.2)	15		
Bilaterality					<0.001*
Present	142/472 (30.1)	110/222(49.5)	252		
Absent	330/472 (69.9)	112/222(50.5)	442		
Multifocality					0.092
Present	287/472(60.8)	120/222(54.1)	407		
Absent	185/472 (39.2)	102/222(45.9)	287		
ETE					<0.001*
Present	360/472 (76.3)	205/222(92.3)	565		
Absent	112/472 (23.7)	17/222(7.7)	129		
TNM stage					0.032
I	389/472 (82.4)	197/222(88.7)	586		
II	83/472 (17.6)	25/222(11.3)	108		
HT					0.935
Present	67/472 (14.2)	31/222(14.0)	98		

Absent	405/472 (85.8)	191/222(86.0)	596	0.166
BRAF ^{V600E} mutation				
Positive	46/55 (83.6)	22/31(71.0)	68	
Negative	9/55 (16.4)	9/31(29.0)	18	

ETE: extrathyroidal extension; TNM stage: tumor node metastasis stage; HT: Hashimoto's thyroiditis; *: statistically significant difference.

Table 4 Correlation between clinicopathological characteristics of PTC patients and LNM

Clinicopathological characteristics	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Age (per 10 years)	0.659(0.588-0.740)	<0.001*	0.658(0.581-0.746)	<0.001*
Gender		<0.001*		<0.001*
female	1 (reference)		1 (reference)	
male	2.697(1.875-3.880)		2.580(1.761-3.781)	
Primary tumor size (per 10mm)	2.182(1.745-2.728)	<0.001*	1.770(1.401-2.234)	<0.001*
Bilaterality		<0.001*		0.163
no	1 (reference)		1 (reference)	
yes	1.791(1.326-2.419)		1.345(0.887-2.041)	
Multifocality		<0.001*		0.097
no	1 (reference)		1 (reference)	
yes	1.648(1.246-2.180)		1.387(0.943-2.040)	
ETE		<0.001*		
no	1 (reference)		1 (reference)	<0.001*
yes	2.920(2.164-3.939)		2.004(1.435-2.798)	

LNМ: lymph node metastasis; ETE: extrathyroidal extension; *: statistically significant difference.

Table 5 Correlation between clinicopathological characteristics of PN1 patients and the NMLNs >5

Clinicopathological characteristics	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Age (per 10 years)	0.696(0.607-0.799)	<0.001*	0.678(0.584-0.787)	<0.001*
Gender		0.143	NA	NA
female	1 (reference)			
male	1.302(0.915-1.851)			
Primary tumor size (per 10mm)	1.646(1.374-1.972)	<0.001*	1.399(1.157-1.692)	0.001*
Bilaterality		<0.001*		<0.001*
no	1 (reference)		1 (reference)	
yes	2.768(1.954-3.921)		2.350(1.639-3.369)	
Multifocality		0.469	NA	NA
no	1 (reference)			
yes	1.168(0.767-1.778)			
ETE		<0.001*		0.001*
no	1 (reference)		1 (reference)	
yes	3.817(2.225-6.547)		2.660(1.493-4.738)	

NMLNs: number of metastatic lymph nodes; ETE: extrathyroidal extension; *: statistically significant difference.

Figures

Figure 1

The diagram shows the process of selecting qualified patients for analysis

Figure 2

Forest plot showing the Correlation between clinicopathological characteristics of PTC patients and LNM

Figure 3

Forest plot showing the Correlation between clinicopathological characteristics of PTC patients and the NMLNs>5

Figure 4

RFS according to the LN stage by Kaplan-Meier curves. These showed poorer RFS in the pN1 than pN0 (RFS 100.0% vs 99.3%, P= 0.104).

Figure 5

RFS according to the NMLNs by Kaplan-Meier curves. These showed poorer RFS in the NMLNs >5 than NMLNs ≤5 (RFS 100.0% vs 97.7%, P=0.002).