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# A retrospective study of the clinical features in papillary thyroid microcarcinoma depending on age

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**The aim of this study was to evaluate the clinical features and correlation of neck lymph node involvement of papillary thyroid microcarcinoma (PTMC) according to patients' age. We divided the patients into three groups according to age: young group (< 45 years, $n = 83$), middle group (45–54 years, $n = 80$), and old group (≥55 years, $n = 53$). The clinical features among the different groups were analyzed retrospectively. All of the 216 patients had received radioiodine ablation at least one time. Among these, 84 patients had central lymph node metastasis (CLNM), 11 patients had lateral lymph node metastasis (LLNM), and 26 patients had both CLNM and LLNM. We show that both lymph node metastasis (LNM) and the CLNM rate were significantly higher in young patients compared with old patients ($P = 0.000$ and 0.000, separately). The radioactive iodine curative ratio in younger patients is also lower than that in the other two groups (37.35, 18.75, and 32.08%, separately, $P = 0.029$). Further Bonferroni test among three groups identified that both LNM and the CLNM rate were significantly higher in the young group than in the old group ($P = 0.000$ and 0.000, separately). Logistic regression analysis showed that young [odds ratio (OR): 2.087, 95% confidence interval (CI): 1.013–4.299, $P = 0.046$] and middle age (OR: 4.049, 95% CI: 1.933–8.482, $P = 0.000$), and extrathyroid extension (OR: 1.952, 95% CI: 1.027–3.711, $P = 0.041$) are independent risk factors for neck LNM. Unlike LNM, young age (< 45 years) (OR: 3.667, 95% CI: 1.732–7.761, $P = 0.001$), extrathyroid extension (OR: 2.256, 95% CI: 1.189–4.282, $P = 0.013$), and male sex (OR: 2.057, 95% CI: 1.042–4.061, $P = 0.038$) were found to be independent risk factors for CLNM. However, no independent risk factors were found to be associated with LLNM. The patients with PTMCs had different clinical features according to age. PTMCs in young patients were more aggressive, especially in LNM. Hence, clinicians should consider an individualized treatment according to age in younger patients to achieve better therapeutic efficacy.** *Nucl Med Commun* **39:713–719** 

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## Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, and its incidence has increased rapidly. An estimated 64 300 new thyroid cancer cases were diagnosed in the USA in 2016 [1]. In China, the estimates of new thyroid cancer incident cases and deaths were 143 000 and 6500, respectively. The crude incidence rate was 10.58/100 000 (male: 5.12/100 000, female: 16.32/100 000). That figure will continue to grow at a rate of 20% per year [2]. Papillary thyroid microcarcinoma (PTMC), defined by the WHO as measuring 10 mm or less in maximum diameter, plays an important role in the rapid growth rate of incidence. The percentage of PTMC increased to nearly 50% of all newly detected cases [3]. Widespread use of ultrasonography and fine-needle aspiration cytology has indeed increased the rate of preoperative diagnosis [4]. Increasingly more experts have begun to acknowledge the actual increase in incidence [3,5] with respect to the therapy of PTMC because of its indolent character and better prognosis (disease-specific mortality is <1%) [6]. The 2015 American Thyroid Association (ATA) Management Guidelines state that an active surveillance can be considered an alternative to immediate surgery in certain low-risk patients [7]. However, certain PTMC patients could also present with cervical lymph node, even distant metastasis, at early stage [6]. We carried out a retrospective analysis of a series of 216 patients with PTMC, aiming to evaluate their clinical behavior and outcomes and to determine possible prognostic factors to select patients who should be treated more aggressively and to differentiate them from the vast majority of PTMC patients who should be spared from overtreatment.

To date, several clinical features predicting a poor prognosis of PTMC patients have been identified, including sex, age, extrathyroid extension (ETE), clinical lymph node and/or distant metastasis, and tumor size. Moreover, the age of 45 years is a cutoff in staging has been disputed

for years. Recent authoritative articles consistently recommend that the age of 55 years as the new cutoff to prevent overstaging of patients with low-risk disease while providing a more realistic estimate of prognosis for those who remain at high risk [8–10]. Our study proposed dividing our participants into three groups, and taking 45-year-old as thresholds. By comparing the clinic features of these three age groups, we sought to determine the relationship between age and lymph node metastasis (LNM) and the therapeutic effect of radioactive iodine (RAI). Also, by incorporating other risk factors, we aimed to indicate the independent risk factors for neck LNM in PTMC.

## Patients and methods

### Patient identification

This study was approved by the Institutional Review Board of Tianjin Medical University General Hospital, and formal consent was not required for this research. Two-hundred and sixteen patients with PTMC who had undergone total thyroidectomy and had received at least one $^{131}$I treatment in our department between January 2009 and November 2016 were analyzed retrospective. The surgical procedures included total thyroidectomy + ipsilateral central lymph node dissection (153)/bilateral central lymph node dissection (33)/ipsilateral functional lymph node dissection (22)/bilateral functional lymph node dissection (8). Of these, 121 presented with cervical LNM: 84 central presented with lymph node metastasis (CLNM) only, 11 presented with lateral lymph node metastasis (LLNM) only, and 26 presented with both CLNM and LLNM.

### Methods

#### *Pretherapy preparation*

All patients were asked to avoid seafood and drugs that may affect $^{131}$I uptake of thyroid (e.g. compound iodine solution, probanthine, etc.) 1 month before the treatment to 1 month after treatment. With respect to the $^{131}$I dose, 30–100 mCi was recommended for regular patients, 100–150 mCi for patients with cervical LNM, and 150–200 mCi is generally recommended if distant metastasis exists.

According to the 2015 ATA risk stratification, appropriate thyroid-stimulating hormone (TSH) suppression therapy was administered routinely to all patients included: TSH less than 0.1 mU/l for intermediate–high-risk patients and 0.1–0.5 mU/l for low-risk patients.

*Follow-up and evaluation of the curative effect*: 6–12 months after RAI, all patients would go back to out-patient department to evaluate related characteristics. Patients' data including general condition, self-conscious symptoms, physical signs, related serological examination, thyroid and cervical lymph node color ultrasound, and whole-body iodine scan were recorded in detail. One year after RAI, the curative effect was evaluated through follow-up data and related examination; the result was classified into two categories: (a) clinical recovery: (i) no clinical evidence of tumor presence; (ii) no imaging evidence of tumor presence; (iii) no $^{131}$I uptake was detected in and out of the thyroid bed in whole-body iodine scan; and (iv) no thyroglobulin antibody (TgAb) interference and serum thyroglobulin (Tg) detected under TSH depression, Tg less than 1 μg/l under TSH stimulation. (b) Nonclinical recovery: any of the above four items does not match.

### Statistical analysis

The statistical analysis was carried out using SPSS software, version 22.0 (IBM, Armonk, New York, USA). The $\chi^2$-Test was used to evaluate differences between categorical variables. A *t*-test and analysis of variance were used to evaluate differences between continuous variables. Data with a non-normal distribution were tested using the Mann–Whitney *U*-test. Variables with a *P* value less than 0.1 in the univariate analyses were included in the multivariate analyses. Binary logistic regression analysis was carried out to identify the multivariate correlates of LNM, CLNM, and LLNM. A *P* value of less than 0.05 was considered statistically significant.

## Results

A total of 216 patients were identified. For the 121 patients with LNM, 84 had CLNM only, 11 had LLNM only, and 26 had both CLNM and LLNM. Table 1 shows the clinicopathological features of the three age groups: young group (age < 45 years), middle group (age = 45–54 years), and old group (age ≥ 55 years). The three groups did not show statistical differences in sex, tumor size, multifocality, thyroid lobe involvement, ETE, concomitant disease (Hashimoto thyroiditis, Graves' disease, nodular goiter), preoperative TSH, Tg, and TgAb ($P > 0.05$). With respect to LNM and CLNM, they showed statistical differences respectively ($P = 0.001$ and 0.001, separately). Further, the Bonferroni test (Table 2) among the three groups showed that both LNM and CLNM rates were significantly higher in young patients (<45 years) compared with old patients (≥55 years) ($P = 0.000$ and 0.000, separately). Statistical difference was found between young and middle age patients ($P = 0.008$). Middle age patients showed a more sensitive tendency toward RAI, especially compared with young patients.

With respect to lymph node metastasis, between LNM(+) and LNM(−) groups, other than age ($P = 0.001$), sex ($P = 0.038$), tumor size ($P = 0.030$), and preoperative TgAb ($P = 0.024$) were significantly different. The LNM-positive group included more male patients, had larger tumor size, and had higher TgAb levels (Table 3). All of the above univariate analyses ($P < 0.1$) were arranged to binary logistic regression model [LNM(−) = 0, LNM(+) = 1; old age = 1, middle = 2, young = 3; female = 0, male = 1; size ≤0.5 = 0, size > 0.5 = 1; TgAb < 40 IU/l = 0, TgAb ≥ 40 IU/l = 1]. Logistic regression analysis showed that young (<45 years)

**Table 1** **Clinicopathological features of the three age groups**

| Characteristics | *n* (%) | | | | *P* value |
|---|---|---|---|---|---|
| | A (< 45 years) | B (45–54 years) | C (≥55 years) | Total | |
| Sex | | | | | |
| Male | 24 (11.1) | 18 (8.3) | 9 (4.2) | 51 (23.6) | 0.267 |
| Female | 59 (27.3) | 62 (28.7) | 44 (20.4) | 165 (76.4) | |
| Size (mean ± SD) (cm) | 0.72 ± 0.23 | 0.66 ± 0.26 | 0.69 ± 0.27 | 0.69 ± 0.25 | 0.250 |
| Size (cm) | | | | | |
| ≤ 0.5 | 18 (8.3) | 27 (12.5) | 21 (9.7) | 66 (30.6) | 0.063 |
| > 0.5 | 65 (30.1) | 53 (24.5) | 32 (14.8) | 150 (69.4) | |
| Multifocality | | | | | |
| Single | 29 (13.4) | 31 (14.4) | 24 (11.1) | 84 (38.9) | 0.483 |
| Multi | 54 (25) | 49 (22.7) | 29 (13.4) | 132 (61.1) | |
| Thyroid lobe involvement | | | | | |
| Unilateral | 31 (14.4) | 30 (13.9) | 19 (8.8) | 80 (37.0) | 0.979 |
| Bilateral | 52 (24.1) | 50 (23.1) | 34 (15.7) | 136 (63.0) | |
| ETE | | | | | |
| No | 58 (26.9) | 61 (28.2) | 35 (16.2) | 154 (71.3) | 0.415 |
| Yes | 25 (11.6) | 19 (8.8) | 18 (8.3) | 62 (28.7) | |
| Combining GD | | | | | |
| No | 80 (37.0) | 78 (36.1) | 50 (23.1) | 208 (96.3) | 0.639 |
| Yes | 3 (1.4) | 2 (0.9) | 3 (1.4) | 8 (3.7) | |
| Combining HD | | | | | |
| No | 61 (28.2) | 62 (28.7) | 40 (18.5) | 163 (75.5) | 0.838 |
| Yes | 22 (10.2) | 18 (8.3) | 13 (6.0) | 53 (24.5) | |
| Combining nodular goiter | | | | | |
| No | 53 (24.5) | 41 (19.0) | 28 (13.0) | 122 (56.5) | 0.222 |
| Yes | 30 (13.9) | 39 (18.1) | 25 (11.6) | 94 (43.5) | |
| Preoperative TSH (mean ± SD) (mIU/l) | 3.86 ± 10.54 | 3.93 ± 15.41 | 2.43 ± 1.46 | 3.55 ± 11.71 | 0.780 |
| Preoperative (mean ± SD)Tg (IU/ml) | 51.26 ± 77.92 | 54.46 ± 78.49 | 41.98 ± 54.90 | 50.4 ± 73.26 | 0.681 |
| Preoperative TgAb (mean ± SD) (IU/l) | 54.11 ± 127.73 | 42.75 ± 113.26 | 81.31 ± 158.70 | 55.58 ± 129.97 | 0.321 |
| LNM | | | | | |
| − | 25 (11.6) | 37 (17.1) | 33 (15.3) | 95 (44.0) | **0.001** |
| + | 58 (26.9) | 43 (19.9) | 20 (9.3) | 121 (56.0) | |
| CLNM | | | | | |
| − | 29 (13.4) | 42 (19.4) | 35 (16.2) | 106 (49.1) | **0.001** |
| + | 54 (25) | 38 (17.6) | 18 (8.3) | 110 (50.9) | |
| LLNM | | | | | |
| − | 66 (30.6) | 65 (30.1) | 48 (22.2) | 179 (82.9) | 0.221 |
| + | 17 (7.87) | 15 (6.9) | 5 (2.31) | 37 (17.1) | |
| Distant metastasis | | | | | |
| No | 82 (38.0) | 79 (36.5) | 51 (23.6) | 212 (98.1) | 0.541 |
| Yes | 1 (0.5) | 1 (0.5) | 2 (0.9) | 4 (1.9) | |
| Number of RAI (mean ± SD) | 1.65 ± 0.85 | 1.61 ± 0.68 | 1.62 ± 0.74 | 1.65 ± 0.77 | 0.948 |
| Cure or not | | | | | |
| Yes | 52 (24.1) | 65 (30.1) | 36 (16.7) | 153 (70.8) | **0.029** |
| No | 31 (14.4) | 15 (6.9) | 17 (7.9) | 63 (29.2) | |

CLNM, central lymph node metastasis; ETE, extrathyroid extension; GD, Graves' disease; HD, Hashimoto's thyroiditis; LLNM, lateral lymph node metastasis; LNM, neck lymph node metastasis; RAI, radioactive iodine; Tg, thyroglobulin; TgAb, thyroglobulin antibodies; TSH, thyroid-stimulating hormone.
Bold values indicate the probability that the differences between samples are due to sampling errors.

**Table 2** **Bonferroni test among the three age groups**

| | A vs. B | B vs. C | A vs. C |
|---|---|---|---|
| LNM | 0.034 | 0.070 | 0.000* |
| CLNM | 0.024 | 0.122 | 0.000* |
| Cure or not | 0.008* | 0.078 | 0.530 |

CLNM, central lymph node; LNM, neck lymph node metastasis.
*$P < 0.0167$ is considered to indicate a statistical difference.

[odds ratio (OR): 2.087, 95% confidence interval (CI): 1.013–4.299, $P = 0.046$] and middle (45–54 years) age (OR: 4.049, 95% CI: 1.933–8.482, $P = 0.000$), and ETE (OR: 1.952, 95% CI: 1.027–3.711, $P = 0.041$) are independent risk factors for neck LNM (Table 4).

With respect to CLNM and LLNM, a similar method was used to analyze clinicopathological features between lymph node positivity and negativity. With respect to CLNM, age ($P = 0.001$), sex ($P = 0.024$), tumor size ($P = 0.014$), ETE ($P = 0.025$), and preoperative TgAb ($P = 0.013$) were significantly different between CLNM (+) and CLNM(−). However, for LLNM, no variable was found to be statistically significant between LLNM(+) and LLNM(−) (Table 5). As shown above, a binary logistic regression model was established to analyze independent risk factors for CLNM and LLNM. Unlike LNM, young age (< 45 years) (OR: 3.667, 95% CI:1.732–7.761, $P = 0.001$), ETE (OR: 2.256, 95% CI: 1.189–4.282, $P = 0.013$), and male sex (OR: 2.057, 95% CI: 1.042–4.061, $P = 0.038$) were found to be independent risk factors for CLNM. However, no independent risk factors were found to be associated with LLNM (Table 6).

**Table 3 Univariate analysis for the occurrence of neck lymph node metastasis**

| Characteristics | *n* (%) | | Univariate analysis *P* value |
|---|---|---|---|
| | LNM negative | LNM positive | |
| Age (mean ± SD) (years) | 49.58 ± 9.84 | 44.51 ± 10.71 | **0.000** |
| Age (years) | | | |
| < 45 | 25 (11.6) | 58 (26.9) | **0.001** |
| 45–54 | 37 (17.1) | 43 (19.9) | |
| ≥ 55 | 33 (15.3) | 20 (9.3) | |
| Sex | | | |
| Male | 16 (7.4) | 35 (16.2) | **0.038** |
| Female | 79 (36.6) | 86 (39.8) | |
| Size (mean ± SD) (cm) | 0.65 ± 0.26 | 0.72 ± 0.24 | **0.030** |
| Size (cm) | | | |
| ≤ 0.5 | 35 (16.2) | 31 (14.3) | 0.076 |
| > 0.5 | 60 (27.8) | 90 (41.7) | |
| Multifocality | | | |
| Single | 37 (17.1) | 47 (21.8) | 0.988 |
| Multi | 58 (26.9) | 74 (34.2) | |
| Thyroid lobe involvement | | | |
| Unilateral | 37 (17.1) | 43 (19.9) | 0.606 |
| Bilateral | 58 (26.9) | 78 (36.1) | |
| ETE | | | |
| No | 74 (34.3) | 80 (37.0) | 0.058 |
| Yes | 21 (9.7) | 41 (19.0) | |
| Combining GD | | | |
| No | 92 (42.6) | 116 (53.7) | 0.989 |
| Yes | 3 (1.4) | 5 (2.3) | |
| Combining HD | | | |
| No | 73 (33.8) | 90 (41.7) | 0.676 |
| Yes | 22 (10.2) | 31 (14.3) | |
| Combining nodular goiter | | | |
| No | 49 (22.7) | 73 (33.8) | 0.198 |
| Yes | 46 (21.3) | 48 (22.2) | |
| Preoperative TSH (mean ± SD) (mIU/l) | 2.12 ± 1.31 | 4.85 ± 16.08 | 0.106 |
| Preoperative Tg (mean ± SD) (IU/ml) | 54.89 ± 75.13 | 46.41 ± 71.70 | 0.444 |
| Preoperative TgAb (mean ± SD) (IU/l) | 32.70 ± 85.43 | 75.54 ± 156.73 | **0.024** |

CLNM, central lymph node metastasis; ETE, extrathyroid extension; GD, Graves' disease; HD, Hashimoto's thyroiditis; LLNM, lateral lymph node metastasis; LNM, neck lymph node metastasis; RAI, radioactive iodine; Tg, thyroglobulin; TgAb, thyroglobulin antibodies; TSH, thyroid-stimulating hormone.
Bold values indicate the probability that the differences between samples are due to sampling errors.

**Table 4 Multivariate logistic regression analysis factors associated with the occurrence of neck lymph node metastasis**

| Predictive factors | B | *P* | OR | 95% CI of OR | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Age (45–54 years) | 0.735 | **0.046** | 2.087 | 1.013 | 4.299 |
| Age (< 45 years) | 1.399 | **0.000** | 4.049 | 1.933 | 8.482 |
| ETE | 0.669 | **0.041** | 1.952 | 1.027 | 3.711 |

CI, confidence interval; ETE, extrathyroid extension; OR, odds ratio.
Bold values indicate the probability that the differences between samples are due to sampling errors.

## Discussion

The age cutoff of 45 years has been used by most of the major thyroid cancer staging systems in well-differentiated thyroid cancer for many years as it represents the median age of most large cohorts upon which such staging systems are based. This has been challenged frequently over recent years with increasingly more robust evidences being reported. Recursive partitioning was performed by Nixon *et al.* [8] to identify the risk factors most predictive of disease-specific survival of PTC. It was found that an age cutoff of 55 years was identified to be the most predictive of survival and was more suitable as the cutoff than the age of 45 years [8]. This was confirmed by the same author with an article covering 10 institutions internationally. They concluded that a change in the cutoff age in the current AJCC/UICC staging system from 45 to 55 years would lead to a downstaging of 12% of patients, and would improve the statistical validity of the model. Such a change would be clinically relevant for thousands of patients worldwide by preventing overstaging of patients with low-risk disease while providing a more realistic estimate of prognosis for those who remain at high risk [9]. When age was adjusted with sex, Jonklaas *et al.* [10] found that although the overall outcome of women with PTC is similar to that of men, this composite outcome is composed of two periods with different outcomes. The first is a period with better outcomes for women than men diagnosed at ages younger than 55 years, whereas the second is a period with similar outcomes for both women and men diagnosed when older than 55 years of age. The age group with the most favorable outcome also corresponds to the age group with the highest incidence of thyroid cancer. They argued that incorporating an age cutoff of 55 years may refine the performance of some DTC staging systems [10].

For PTMC patients, it is unclear whether an age cutoff of 45 years or 55 years is more appropriate to predict overall survival. LNM is one of the main predictors of recurrence and survival. Our study divided our participants into three different groups (< 45, 45–54, ≥ 55 years) on the basis of these two disputed age cutoffs. On comparing the clinicopathological features of groups, we did not find statistical differences in sex, tumor size, multifocality, thyroid lobe involvement, ETE, concomitant disease (Hashimoto thyroiditis, Graves' disease, nodular goiter), Preoperative TSH, Tg, and TgAb. However, compared with old patients (≥55 years), LNM and CLNM rates were significantly higher in young patients (< 45 years). On incorporating other risk factors affecting LNM and CLNM, we found that patients in young and middle groups, and ETE are independent risk factors for neck LNM. Patients in the young group, ETE, and male sex were found to be independent risk factors for CLNM.

Although young age is currently considered to lead to a good prognosis in the AJCC/UICC TNM staging system, our study showed that younger patients were more likely to develop neck LNM. The risk age cutoffs for LNM and CLNM were 55 and 45 years, respectively. Our results are partly in agreement with several past reports. Oh and colleagues reported that large volume LNM was more frequently found in young (< 40 years) and male patients. They suggested more aggressive therapeutic

**Table 5 Univariate analysis for the occurrence of lymph node metastasis (CLNM + LLNM)**

| Characteristics | CLNM negative [*n* (%)] | CLNM positive [*n* (%)] | Univariate analysis *P* value | LLNM negative [*n* (%)] | LLNM positive [*n* (%)] | Univariate analysis *P* value |
|---|---|---|---|---|---|---|
| Age (mean ± SD) (years) | 49.17 ± 9.88 | 44.40 ± 10.82 | **0.001** | 47.28 ± 10.43 | 44.14 ± 11.26 | 0.101 |
| Age (years) | | | | | | |
| < 45 | 29 (13.4) | 54 (25) | **0.001** | 66 (30.6) | 17 (78.7) | 0.221 |
| 45–54 | 42 (19.4) | 38 (17.6) | | 65 (30.1) | 15 (6.9) | |
| ≥ 55 | 35 (16.2) | 18 (8.3) | | 48 (22.2) | 5 (2.3) | |
| Sex | | | | | | |
| Male | 18 (8.3) | 33 (15.3) | **0.024** | 38 (17.6) | 13 (6.0) | 0.070 |
| Female | 88 (40.7) | 77 (35.6) | | 141 (65.3) | 24 (11.1) | |
| Size (mean ± SD) (cm) | 0.65 ± 0.25 | 0.73 ± 0.24 | **0.014** | 0.68 ± 0.25 | 0.74 ± 0.24 | 0.184 |
| Size (cm) | | | | | | |
| ≤ 0.5 | 39 (18.1) | 27 (12.5) | 0.051 | 58 (26.9) | 8 (3.7) | 0.195 |
| > 0.5 | 67 (31.0) | 83 (38.4) | | 121 (56.0) | 29 (13.4) | |
| Multifocality | | | | | | |
| Single | 40 (18.5) | 44 (20.4) | 0.733 | 72 (33.3) | 12 (5.6) | 0.376 |
| Multi | 66 (30.6) | 66 (30.6) | | 107 (49.5) | 25 (11.6) | |
| Involving the thyroid lobe | | | | | | |
| Unilateral | 40 (18.5) | 40 (18.5) | 0.835 | 66 (30.6) | 14 (6.5) | 0.912 |
| Bilateral | 66 (30.6) | 70 (32.4) | | 113 (52.3) | 23 (10.6) | |
| ETE | | | | | | |
| No | 83 (38.4) | 71 (32.9) | **0.025** | 132 (6.1) | 22 (10.2) | 0.080 |
| Yes | 23 (10.6) | 39 (18.1) | | 47 (21.8) | 15 (6.9) | |
| Combining GD | | | | | | |
| No | 102 (47.2) | 106 (49.1) | 1.000 | 172 (79.6) | 36 (16.7) | 1.000 |
| Yes | 4 (1.9) | 4 (1.9) | | 7 (3.2) | 1 (0.5) | |
| Combining HD | | | | | | |
| No | 79 (36.6) | 84 (38.9) | 0.754 | 139 (64.4) | 24 (11.1) | 0.100 |
| Yes | 27 (12.5) | 26 (12.0) | | 40 (18.5) | 13 (6.0) | |
| Combining nodular goiter | | | | | | |
| No | 56 (25.9) | 66 (30.6) | 0.288 | 96 (44.4) | 26 (12.0) | 0.063 |
| Yes | 50 (23.1) | 44 (20.4) | | 83 (38.4) | 11 (5.1) | |
| Preoperative TSH (mIU/l) | 2.17 ± 1.31 | 5.07 ± 16.81 | 0.116 | 3.72 ± 12.73 | 2.66 ± 1.76 | 0.661 |
| Preoperative (mean ± SD) Tg (IU/ml) | 53.35 ± 72.72 | 47.35 ± 74.13 | 0.588 | 52.38 ± 74.95 | 39.64 ± 63.24 | 0.407 |
| Preoperative TgAb (mean ± SD) (IU/l) | 31.41 ± 82.18 | 80.87 ± 162.60 | **0.013** | 53.68 ± 129.93 | 66.08 ± 132.15 | 0.649 |

CLNM, central lymph node metastasis; ETE, extrathyroid extension; GD, Graves' disease; HD, Hashimoto's thyroiditis; LLNM, lateral lymph node metastasis; LNM, neck lymph node metastasis; RAI, radioactive iodine; Tg, thyroglobulin; TgAb, thyroglobulin antibodies; TSH, thyroid-stimulating hormone.
Bold values indicate the probability that the differences between samples are due to sampling errors.

**Table 6 Multivariate logistic regression analysis factors associated with the occurrence of central lymph node metastasis**

| | | | | 95% CI of OR | |
|---|---|---|---|---|---|
| Predictive factors | *B* | *P* | OR | Lower | Upper |
| Age (45–54 years) | 0.639 | 0.092 | 1.894 | 0.901 | 3.982 |
| Age (< 45 years) | 1.299 | **0.001** | 3.667 | 1.732 | 7.761 |
| Sex | 0.721 | **0.038** | 2.057 | 1.042 | 4.061 |
| ETE | 0.814 | **0.013** | 2.256 | 1.189 | 4.282 |

CI, confidence interval; ETE, extrathyroid extension; OR, odds ratio.
Bold values indicate the probability that the differences between samples are due to sampling errors.

options for these patients [11]. Miyauchi [12] reported that patients 40 years of age or younger tended to show progression of the disease during active observation of PTMC, although patients with these slight progressions of the disease could be treated successfully with a rescue surgery. Ito *et al.* [13] divided their patients into three subsets on the basis of age at the beginning of observation: young (< 40 years), middle-aged (40–59 years), and old patients (≥60 years). The proportion of patients with PTMC progression was the lowest among the old patients and the highest among the young patients. A multivariate analysis found that young age was an independent predictor of PTMC progression. They suggested that old patients with subclinical low-risk PTMC may be the best candidates for observation. Siddiqui *et al.* [14] found that age younger than 45 years, along with multifocality and ETE, significantly increased the risk of central CLNM. These results are basically in line with our research, although the age cutoffs are not exactly the same.

Apart from age, our study showed that ETE was an independent risk factor for LNM. ETE and male sex were independent risk factors for CLNM. Both the risk factors have been reported by other authors in recent years. Gui *et al.* [15], who studied 541 PTMC patients in a single institution, concluded that CLNM was associated with male sex, younger age (< 45 years), larger tumor size (>0.575 cm), ETE, and multifocal PTMC. As mentioned above, Siddiqui *et al.* [14] found that age younger than 45 years along with multifocality and ETE significantly increased the risk of central CLNM. Lee and colleagues studied 2930 PTC patients from a single

institution, and reported that recurrence and death were more common among male patients with PTC than female patients with PTC. However, there was no difference in disease-free survival between male and female PTMC patients [16]. A recent meta-analysis including 1586 PTMCs showed that multifocality is associated significantly with the risk of LNM [17]. According to current researches, it seemed that almost all the risk factors that we mentioned above including sex, tumor size, multifocality, bilateral lob involvement, and ETE have been reported to be associated with prognosis in PTMC, but which of these indeed affect the prognosis in PTC or PTMC is still unclear. We strongly recommend more multicenter randomized-controlled studies to address this question in the future.

With respect to RAI therapy, the ATA [7] classifies thyroid cancer patients into low-risk, intermediate-risk, and high-risk groups on the basis of their relative rates of recurrence and mortality. RAI is recommended for high-risk patients with gross ETE, distant metastasis, or incomplete tumor resection. For unifocal and multifocal PTMC without other adverse features, RAI was not recommended routinely. Because of low-quality evidence and the lack of long-term prognosis analysis, the guidelines made only a weak recommendation for intermediate-risk differentiated thyroid carcinoma. However, distant metastases and death (0.4–1% annually) have recently been reported to result from PTMC progression, which indicated that a more aggressive treatment should be adopted in PTMCs [18]. Gao *et al.* [19], who studied 280 cases of PTMC treatment with radioiodine, found 40 (14.3%) cases with persistent disease and one patient (0.4%) with distant metastasis. This indicated that smaller tumor size ($\leq 1$ cm) was not equivalent to low risk. Creach *et al.* [20], who studied 349 postoperative PTMC patients who underwent RAI treatment, found that the 5-year recurrence-free survival for patients with RAI treatment was significantly higher than without RAI treatment, especially the patients with LNM. Xue and colleagues found that the disease-free survival period was significantly shorter for the RAI(−) patients than for the RAI(+) patients. It was concluded that RAI may be beneficial for PTMC with LLNM, especially when the CLNM rate and/or the LLNM rate was greater than 0.5 [21]. However, to date, it is still unclear as to which patients may benefit from RAI treatment in PTMC. In our research, a statistical difference was found between young and middle-age patients. Middle-age patients (45–54 years) showed a more sensitive tendency toward RAI treatment, especially compared with young patients. Is there a cutoff age associated with RAI treatment sensitivity in PTMC? We believe that further studies should be carried out to answer this question.

## Conclusion

Patients with PTMCs had different clinical features according to age. PTMCs in young patients were more aggressive, especially with LNM. Hence, clinicians should consider an individualized treatment according to age to achieve better therapeutic efficacy.

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### Conflicts of interest

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