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The impact of age at diagnosis on central lymph node metastasis in clinically low-risk papillary thyroid microcarcinoma patients

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Abstract

Background Age is an independent risk factor for central lymph node metastasis (CLNM) in clinically negative lymph node (cN0) papillary thyroid microcarcinoma (PTMC) patients. The objective of this study was to investigate the impact of age on CLNM in clinically low-risk PTMC patients.

Methods A retrospective analysis was performed on patients with clinically low-risk PTMC who underwent surgery between January 2016 and December 2018. Logistic regression analysis was used to examine the impact of age on the risk of CLNM. The associations between age and pN1a and the lymph node ratio (LNR) were examined by a restricted cubic spline (RCS) curve with logistic regression models.

Results A total of 1352 patients (mean [range] age, 43[18-76] years; 325 males [24.0%]) were enrolled in this study. Logistic regression analysis revealed that age was a significant factor influencing the risk of CLNM (OR 0.95, 95% CI 0.94–0.96; $p < 0.001$). The RCS curve revealed a significant nonlinear association between age and pN1a status and the LNR. For patients under the age of 55, the risk of CLNM (OR 0.59, 95% CI 0.55–0.65, $p < 0.001$) and the LNR (beta −0.23, 95% CI -0.27, -0.19, $p < 0.001$) significantly decreased as age increased. For patients aged ≥ 55 years, the risk of LNM (OR 1.03, 95% CI 0.81–1.32; $p = 0.79$) and the LNR (Beta −0.03, 95% CI -0.07,0.13, $p = 0.54$) did not change with age.

Conclusions This study confirmed that age was a significant factor influencing the risk and severity of CLNM in patients with low-risk PTMC. The risk and severity of LNM were lowest in patients aged ≥ 55 years.

Keywords Papillary thyroid microcarcinoma, Low-risk, Central lymph node metastasis, Age

Papillary thyroid microcarcinoma (PTMC) is defined as a papillary thyroid carcinoma measuring ≤ 10 mm in greatest dimension [1]. PTMC has contributed significantly to the increased incidence of papillary cancer in recent decades [2]. Active surveillance (AS) has been suggested as an appropriate initial approach for clinically low-risk PTMC patients given its favorable prognosis [3, 4]. Furthermore, the literature suggests that age is a crucial indicator of progression in patients with low-risk PTC under AS. Several prospective studies have shown that younger individuals are more likely to experience disease progression [5, 6]. Thus, guidelines recommend that AS is ideal

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for patients aged 60 years and older but not for younger patients [3, 7, 8].

Previous studies revealed that the incidence of central lymph node metastasis (CLNM) was approximately 18.3–50.0% in clinically negative lymph node (cN0) PTMC patients [9–11]. Although some studies have shown that CLNM does not affect overall survival, studies have reported that lymph node metastasis is associated with increased local recurrence rates and decreased recurrence-free survival rates [12, 13]. Extranodal extension (ENE) is recognized as a significant prognostic factor for PTC [14], and microscopic ENE has also been identified as an independent risk factor for locoregional recurrence [15]. Patient age has been proven to be one of the independent risk factors associated with CLNM in patients with cN0 PTC [9, 16–19]. And, some genetic alterations, such as BRAF mutations and TERT promoter mutations, are also associated with increased clinical aggressiveness of PTC [20, 21]. At present, there is limited research focusing on occult lymph node metastasis in clinically low-risk PTMC patients. Determining the status of lymph nodes is crucial in making informed decisions regarding the treatment of clinically low-risk PTMC. This information may significantly contribute to developing personalized treatment and care strategies.

In this study, we conducted a retrospective analysis to investigate the impact of age at diagnosis on occult central lymph node metastasis in patients with clinically low-risk PTMC treated with surgery. We aimed to gain a better understanding of the role of age at diagnosis in decision-making for the management of clinically low-risk PTMC patients.

Materials and methods

Patients

We conducted a retrospective analysis of a cohort of patients who underwent initial surgery for PTMC at a cancer center between January 2016 and December 2018. Patients who met the eligibility criteria for initial thyroid lobectomy in the National Comprehensive Cancer Network (NCCN) guidelines [22] and for active surveillance as recommended by the American Thyroid Association (ATA) thyroid cancer management guidelines [23] were enrolled in the study. Patients with bilateral tumors, multifocal tumors identified on preoperative ultrasound examination, gross extrathyroidal extension (gETE) identified on preoperative imaging, clinical LNM, gross ENE (identified preoperatively if the metastatic lymph nodes were fused together or invaded nearby tissues or structures, such as the recurrent laryngeal nerve, strap muscles, trachea, or esophagus), distant metastases, a history of radiation therapy on the neck, or a history of familial thyroid cancer were excluded. Patients with incomplete demographic data or pathological results were also excluded. All the included patients underwent lobectomy (with isthmectomy) and ipsilateral central neck dissection. Postoperative treatments included appropriate levels of thyrotropin suppression.

Data collection

Data, including age, sex, and pathological characteristics, were obtained from medical records. Pathological diagnosis was determined based on standard World Health Organization criteria [24]. The pathological characteristics included histological variant, tumor location (lower, middle, upper or multifocal), tumor size, Hashimoto's thyroiditis (HT), multifocality, microscopic ETE (mETE), lymphovascular invasion (LVI), cervical lymph node status (pN stage, number of metastatic lymph nodes [LNs] and ENE). The clinical lymph node status was primarily evaluated through preoperative ultrasound (US) examination [25]. Additionally, any palpable firm lymph nodes, evidence of lymph node fusion, or identification of invasive lymph nodes during surgery were considered clinical LNM. In this study, LNM with ≥ 5 metastatic lymph nodes (LNs) or ENE was defined as high-risk LNM. The lymph node ratio (LNR) was defined as the number of metastatic LNs divided by the total number of LNs. Restaging was performed using the American Joint Committee on Cancer TNM Stage for Thyroid Cancer (8th Edition, 2017) [26]. The initial risk stratification was performed in accordance with the 2015 ATA guidelines [23].

Statistical analysis

We selected age cutoff points of 30 and 55 years, and the entire patient cohort was divided into three groups according to their age distribution: ≤30 years (young patients), 31–54 years (middle-aged patients), and ≥ 55 years (older patients). Categorical variables are expressed as frequencies and proportions, and the chi-square test or Fisher's exact test was used for comparisons. Continuous variables are presented as the mean ± standard deviation and median and were compared with one-way ANOVA. Multivariate logistic regression analysis was used to examine the impact of age at diagnosis on the risk of lymph node metastasis. The confounding variables included sex, tumor location, tumor size, aggressive variant, LVI, HT and mETE. The associations between age and pN stage and the LNR were examined by a restricted cubic spline (RCS) curve with logistic regression models. A two-piecewise logistic regression model was used on both sides of the inflection point, and a log likelihood ratio test was performed. In our study, all the statistical analyses were performed using R software, version 4.2.2, and the Match It package along with the use of MSTATA software. All the statistical tests were two-sided, and a P value of less than 0.05 indicated statistical significance.

Results

Demographic and pathological characteristics

A total of 1352 patients who met the inclusion criteria were enrolled in this study. Among them, 325 (24.0%) were male. The mean age was 43 years (range 18 to 76 years). The mean tumor size was 0.61 cm (range 0.1–1.0 cm). A total of 328 patients (25.0%) had coexisting HT. Aggressive variants, LVI, and mETE were present in 12 (0.9%), 5 (0.4%) and 467 (34.5%) patients, respectively. A total of 487 patients (36.0%) had pathological CLNM (pN1a). Fifty (3.7%) patients had 5 or more metastatic LNs. Forty-three patients (3.2%) had ENE, and 85 patients (6.3%) had high-risk LNM. The mean LNR was 0.14. A total of 1310 patients (96.9%) were classified as stage I, and 42 patients (3.1%) were classified as stage II. According to the 2015 ATA risk stratification system, 856 patients (63.3%) were classified as low risk, and 496 patients (36.7%) were classified as intermediate risk. The details of the characteristics are presented in Table 1. There were no significant differences among the groups in terms of sex, tumor location, tumor size, HT, aggressive variant or LVI (p>0.05). The proportion of patients with mETE was greatest in the older group and lowest in the young group, but the difference was not significant ($p = 0.09$). The proportion of pN1a stage was highest in young patients (54.9%) and lowest in older patients (21.1%). Similarly, the number of metastatic LNs (1.43 ± 1.81) and the LNR (0.24 ± 0.30) were highest in young patients and lowest in older patients (0.43 ± 1.08 and 0.07 ± 0.19, respectively). The proportion of high-risk LNM was highest in young patients (12.1%) and lowest in older patients (4.0%). All of these differences were statistically significant.

Impact of age on lymph node metastasis

Logistic regression analysis revealed that age was a significant factor influencing the risk of CLNM (OR 0.95, 95% CI 0.94–0.96, $p < 0.001$) after adjusting for confounding variables. Additionally, older patients (OR 0.22, 95% CI 0.14–0.34, $p < 0.001$) and middle-aged patients (OR 0.46, 95% CI 0.33–0.63, $p < 0.001$) were found to have a significantly lower risk of CLNM than young patients (Table 2).

Table 1 Patient demographics and baseline characteristics

Characteristic		Overall, $N = 1,352$[1]	Age group			Statistic	p-value
			≤ 30years, $N = 173$[1]	31–54 years, $N = 980$[1]	≥ 55 years, $N = 199$[1]		
Age, years	Mean ± SD	43 ± 10	27 ± 2	42 ± 7	59 ± 4	-	-
	Range	18, 76	18, 30	31, 54	55, 76		
Male sex		325 (24.0%)	53 (30.6%)	231 (23.6%)	41 (20.6%)	5.53	0.063[2]
Tumor size, cm	Mean ± SD	0.61 ± 0.20	0.62 ± 0.21	0.60 ± 0.20	0.62 ± 0.21	1.10	0.332[3]
	Range	0.1, 1.0	0.1, 1.0	0.1, 1.0	0.1, 1.0		
Tumor location	upper	282 (20.9%)	28 (16.2%)	209 (21.3%)	45 (22.6%)	5.73	0.454[2]
	middle	614 (45.4%)	84 (48.6%)	441 (45.0%)	89 (44.7%)		
	lower	289 (21.4%)	40 (23.1%)	214 (21.8%)	35 (17.6%)		
	multifocal	167 (12.4%)	21 (12.1%)	116 (11.8%)	30 (15.1%)		
Aggressive variant		12 (0.9%)	1 (0.6%)	8 (0.8%)	3 (1.5%)	-	0.629[4]
HT		338 (25.0%)	47 (27.2%)	235 (24.0%)	56 (28.1%)	2.02	0.363[2]
LVI		5 (0.4%)	2 (1.2%)	2 (0.2%)	1 (0.5%)	-	0.088[4]
mETE		467 (34.5%)	51 (29.5%)	336 (34.3%)	80 (40.2%)	4.81	0.090[2]
pN1a stage		487 (36.0%)	95 (54.9%)	350 (35.7%)	42 (21.1%)	46.04	< 0.001[2]
N of mLNs	Mean ± SD	0.82 ± 1.45	1.43 ± 1.81	0.79 ± 1.41	0.43 ± 1.08	23.40	< 0.001[3]
	Range	0, 11	0, 8	0, 11	0, 7		
N of mLNs ≥ 5		50 (3.7%)	14 (8.1%)	31 (3.2%)	5 (2.5%)	10.95	0.004[2]
LNR, Mean ± SD		0.14 ± 0.25	0.24 ± 0.30	0.14 ± 0.24	0.07 ± 0.19	21.20	< 0.001[3]
ENE		43 (3.2%)	9 (5.2%)	31 (3.2%)	3 (1.5%)	4.11	0.128[2]
High-risk LNM		85 (6.3%)	21 (12.1%)	56 (5.7%)	8 (4.0%)	12.34	0.002[2]
TNM stage	I	1,310 (96.9%)	173 (100.0%)	980 (100.0%)	157 (78.9%)	251.15	< 0.001[2]
	II	42 (3.1%)	0 (0.0%)	0 (0.0%)	42 (21.1%)		
ATA risk group	low	856 (63.3%)	115 (66.5%)	624 (63.7%)	117 (58.8%)	2.55	0.280[2]
	intermediate	496 (36.7%)	58 (33.5%)	356 (36.3%)	82 (41.2%)		

[1]n (%), [2]One-way ANOVA, [3]Pearson's Chi-squared test, [4]Fisher's exact test

Abbreviations: SD, standard deviation; HT, Hashimoto's thyroiditis; mETE, microscopic extrathyroidal extension; LVI, lymphovascular invasion; N of mLNs, number of metastatic lymph nodes; LNR, lymph node ratio; LNM, lymph node metastasis; ENE, extranodal extension

Table 2 Association between age group and pN1a stage (logistic regression analysis)

Characteristic	Total	pN1a stage	OR[1]	95% CI[1]	*p*-value
Age group*					
≤ 30 years	173	95	—	—	
31–54 years	980	350	0.46	0.33, 0.63	< 0.001
≥ 55 years	199	42	0.22	0.14, 0.34	< 0.001

[1]OR = Odds Ratio, CI = Confidence Interval

* Multivariate logistic regression analysis was conducted to examine the association between age at diagnosis and the risk of CLNM, adjusting for sex, tumor location, tumor size, aggressive variant, LVI, HT and mETE

Relationships between age at diagnosis and pN1a status and the LNR

We used RCS to create a flexible model and visualized the relationships between age at diagnosis and pN1a and LNR based on a logistic regression model adjusted for the effects of sex, tumor location, tumor size, aggressive variant, LVI, HT and mETE. A significant nonlinear association was observed between age and pN stage (p value for age < 0.001, p value for nonlinearity = 0.006; Fig. 1A) and between age and the LNR (p value for age < 0.001, p value for nonlinearity < 0.001; Fig. 1B). The inflection point of the RCS curve was identified at age = 55. For patients under the age of 55, as age increased, the risk of CLNM (pN1a) showed a significant decreasing trend (OR 0.59, 95% CI 0.55–0.65, $p < 0.001$). In contrast, for patients aged ≥ 55 years, the risk of CLNM did not change with age (OR 1.03, 95% CI 0.81–1.32; $p = 0.79$) (Table 3). For patients under 55 years old, the LNR gradually decreased with age (Beta – 0.23, 95% CI -0.27, -0.19, $p < 0.001$), while for patients aged ≥ 55 years, the LNR did not change with age (Beta 0.03, 95% CI -0.07,0.13, $p = 0.54$) (Table 4).

Discussion

Age at diagnosis has been identified as a significant risk factor for CLNM in patients with cN0 PTMC, and the majority of studies use age 45 or 55 years as a cutoff point, considering patients younger than 45 or 55 years to be at a significantly greater risk [9, 18]. Several researchers have also examined age as a continuous variable and have shown that as age increases, the risk of metastasis

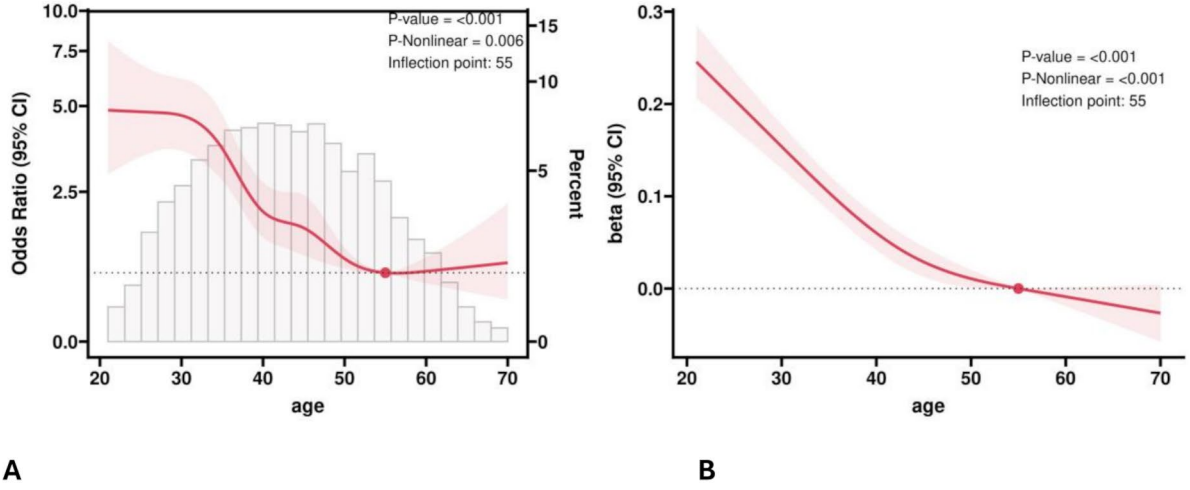

Fig. 1 Association between age and pN stage (**A**) and LNR(**B**) with the RCS function. (**A**) Model with 6 knots at the 5th, 23rd, 41st, 59th, 77th and 95th percentiles. Y-axis represents the OR to present pN1a stage for any value of age compared to individuals with reference value (50th percentile) of age. (**B**) Model with 3 knots at the 10th, 50th and 90th percentiles. Y-axis represents the beta to present LNR for any value of age compared to individuals with reference value (50th percentile) of age. The logistic regression was adjusted for sex, tumor location, tumor size, aggressive variant, LVI, HT and mETE

Table 3 Effect of standardized age on pN stage and the LNR

Characteristic	pN1a stage[1]			LNR[2]		
	OR per SD*	95% CI	*p*-value	Beta per SD*	95% CI	*p*-value
Age (< 55 years)	0.59	0.55, 0.65	< 0.001	-0.23	-0.27, -0.19	< 0.001
Age (≥ 55 years)	1.03	0.81, 1.32	0.79	0.03	-0.07, 0.13	0.54

OR = Odds Ratio, CI = Confidence Interval

* A restricted cubic spline (RCS) curve with logistic regression models was conducted to investigate the associations between age at diagnosis and pN stage and the LNR. A two-piecewise logistic regression model was used on both sides of the inflection point, and both ORs and Betas were adjusted for sex, tumor location, tumor size, aggressive variant, LVI, HT and mETE. [1] Adjusted Odds Ratios from Segmented Logistic Regression Analysis. [2]Adjusted Coefficients from Segmented Linear Regression Analysis

gradually decreases (OR 0.977, 95% CI 0.963–0.992, $p = 0.003$) [16, 17].

Active surveillance (AS) has proven to be safe and effective for low-risk PTMC patients [3, 4]. Several prospective studies have shown that younger patients are more likely to experience disease progression [5, 6, 27]. Therefore, most guidelines suggest using AS for older patients and discourage its use for younger patients but do not offer definitive age-specific recommendations. For example, guidelines from the Japan Association of Endocrine Surgery Task Force recommend AS for older patients and generally advise against it for patients under the age of 18 to 20 [27]. The SBEM (2022) and Korean Thyroid Association (KTA) (2023) guidelines state that AS is ideal for patients aged 60 and above and can be considered appropriate for those aged between 18 and 59 [7, 8]. This may be due to a deficiency in definitive and reliable clinical evidence.

The present study focused on low-risk PTMC patients who met the criteria for AS but who received surgical treatment. We investigated the relationships between age at diagnosis and pathological lymph node metastasis, including LNM rate and the LNR, by employing robust statistical methods. Our findings indicate that younger patients have a highest rate of CLNM, highest number of metastatic LNs and a greater proportion of high-risk LNM. The RCS curve revealed that for patients under the age of 55, the risk of CLNM and the LNR decrease gradually with age, suggesting that young patients may experience faster tumor progression. Therefore, caution should be exercised when considering active surveillance (AS) for younger patients. Conversely, patients aged 55 and older had lowest rates of CLNM, lowest number of metastatic LNs and a lowest proportion of high-risk LNM. Additionally, the RCS curve demonstrated that for patients aged 55 and older, there was no significant change in the risk of LNM or the LNR with increasing age, indicating a stable trend in tumor progression for this age group. This comprehensive analysis not only underscores the potential risk of metastasis but also illuminates the severity of metastasis. The results may provide evidence for the selection of treatment strategies for low-risk PTC patients in terms of age.

Our study has several limitations. Due to the retrospective nature of the data, factors such as sample size and preoperative imaging evaluations (specifically ultrasonography) were not preplanned, and we did not consider differences among surgical operators, which could impact the accuracy of tumor assessment and lead to selection bias. Additionally, data on characteristics such as BRAF status and TERT promoter mutations were not obtained. These limitations could affect the final results and limit the generalizability of the conclusions.

Conclusion

This study revealed that age at diagnosis is a significant factor influencing the risk and severity of CLNM in patients with low-risk PTMC. The risk and severity of CLNM were lowest in older patients (aged ≥ 55 years). In the future, it is necessary to conduct prospective studies to validate the findings of our study and obtain reliable and generalizable conclusions.

Abbreviations

PTMC	Papillary thyroid microcarcinoma
HT	Hashimoto's thyroiditis
ETE	Extrathyroidal extension
mETE	Microscopic extrathyroidal extension
LVI	Lymphovascular invasion
LNM	Lymph node metastasis
CLNM	Central lymph node metastasis
LNs	Lymph nodes
LNR	Lymph node ratio
ENE	Extranodal extension

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None.

Author contributions

Yunhe Liu, Lida Liao and Hui Huang contributed to conception and design of the study. Yunhe Liu, Lida Liao organized the database and performed the statistical analysis. Yunhe Liu, Lida Liao wrote sections of the manuscript and prepared tables. Jie Liu, Wensheng Liu and Shaoyan Liu contributed to manuscript revision. All authors read and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was carried out in accordance with the guidelines and regulations for human research (Helsinki declaration). The study was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences. Informed consent was obtained at the time of surgery for general use of clinical information for future studies.

Consent for publication

Not applicable.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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