



The relationship between central lymph node metastasis and the distance from tumor to thyroid capsule in papillary thyroid microcarcinoma without capsule invasion

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Background: This study aims to explore the predictive factors of central lymph node metastasis (CLNM) in patients with papillary thyroid microcarcinoma (PTMC) without capsule invasion.

Methods: From January 2016 to October 2018, 1,622 patients with PTMC, who underwent surgical treatment at Zhejiang Cancer Hospital, were enrolled in the present study. A model of multivariate logistic regression was developed to find the variables that were independently associated with CLNM. The results were presented in the odds ratio (OR) with a 95% confidence interval (CI). The nomogram for predicting CLNM was developed based on the results of the multivariate logistic regression analysis. The distance (distance >0) from tumor to capsule is defined as the shortest distance from the tumor boundary to the capsule or trachea.

Results: The multivariate logistic regression analysis indicated that age, gender, tumor maximum diameter, tumor mean diameter, and tumor volume were independently associated with CLNM. In the 692 cases without capsular invasion, the distance from the capsule was not correlated to the CLNM. The joint model, which included age, gender, tumor volume, and capsular invasion, were analyzed using the ROC curve. The cut-off point for the prediction of CLNM was defined as a value of 0.208. The area under the ROC curve was 0.687, the sensitivity was 65.4%, and the specificity was 63.3%.

Conclusions: Gender, age, maximum diameter, mean diameter, tumor volume, and capsular invasion were independently associated with the CLNM. When there was no capsular invasion, the distance between the tumor and capsule was not correlated to the CLNM, suggesting that considering whether the tumor is close to the capsule may not be necessary for low-risk PTMC.

Keywords: Papillary thyroid microcarcinoma (PTMC); distance; thyroid capsule; central lymph node metastasis; predictive factors

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Introduction

In recent years, the incidence of thyroid cancer has significantly increased worldwide, and most of which are papillary thyroid carcinomas (PTCs) (1-5). The main reason is the incidence of papillary thyroid microcarcinoma (PTMC, a papillary thyroid with a maximum tumor diameter of ≤ 10 mm), which has rapidly increased (6,7). Therefore, the treatment of PTMC has attracted the attention of researchers. At present, most scholars continue to insist that although PTMC has a good prognosis, most patients still required surgery. The 2015 American Thyroid Association (ATA) recommendations for PTMC requiring surgical treatment indicate that routine preventive dissection of lymph nodes is not recommended for T1 and T2 (8), which differs from the recommendations in the 2016 Chinese expert consensus for central lymph node dissection (9). Therefore, it remains controversial whether to perform prophylactic central lymph node dissection (PCND) in patients with PTMC. To date, no overwhelming evidence has proven whether PCND definitively improves PTMC patient prognosis (10-12). Some researchers have reported that the outcomes of thyroidectomy and thyroidectomy plus PCND are similar for experienced surgeons (13,14). However, many studies have indicated that there is indeed an association between PCND and postoperative complications (15,16). The PCND and postoperative complications of these published studies are summarized in *Table 1*.

Though the PCND postoperative complications have been reduced in recent years, they still occur. Therefore, it is necessary to determine whether patients need PCND. The present study conducted a large sample retrospective study to explore the predictive factors of central lymph node metastasis (CLNM) in patients with PTMC in the Chinese population. There are similar articles (21,27), but they are for PTC patients with tumor of less than 1.5 cm and tumor of 1–3 cm while this study was aimed at PTMC patients. And it is worth mentioning that the distance between tumor and capsule was taken as a parameter.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/gs-20-478>).

Methods

Study design and patients

The study was conducted in accordance with the

Declaration of Helsinki and was approved by Medical Ethics Committee of Zhejiang Cancer Hospital (approval ID: IRB-2020-89). Informed consent was obtained in all cases for the study.

One thousand six hundred twenty-two PTMC cases in Zhejiang Cancer Hospital from January 2016 to October 2018 were enrolled in the present study. Then, the demographic and clinical information of these patients were obtained from the clinical medical records of our hospital. Inclusion criteria: (I) patients with tumor located on one side, with a maximum diameter of ≤ 10 mm; (II) patients who underwent central lymph node dissection; (III) patients with a postoperative pathology confirmed as PTMC; (IV) patients who underwent operations performed by veteran surgeons; (V) patients who underwent an ultrasonography examination in Zhejiang Cancer hospital before undergoing surgery. Exclusion criteria: (I) patients who did not undergo a B-ultrasound examination in our hospital or had missing B-ultrasound images in our hospital; (II) patients who had lesions located on two sides; (III) patients with a lesion maximum diameter of >10 mm under B-ultrasound; (IV) patients who previously received thyroid cancer surgery.

For patients with missing data: these patients were excluded or not included in the present study.

The study parameters included: age, gender, average tumor diameter (the three-dimensional data of the tumor was taken by ultrasonography), while the mean was calculated as the average diameter of the tumor. Tumor volume was calculated with the approximate volume using the sphere volume formula, $V = \pi/6 \times \text{average diameter}^3$, regarding the tumor as the sphere. Capsular invasion and the distance from the capsule were taken on the ultrasonography. Research the correlation between distance and CLNM in patients without capsule invasion. This distance was the shortest distance from the tumor boundary to the capsule or trachea. We measured the distance between tumor and capsule on ultrasound image (double headed arrow (*Figure 1*)). Age was categorized as follows: ≤ 45 and >45 years old. The largest diameter of the tumor was classified as follows: ≤ 5 and >5 mm. The average tumor diameter was classified as follows: ≤ 5 and >5 mm. The tumor volume was classified as follows: ≤ 90 and >90 mm³. The distance from the capsule was classified as follows: 0–1, 1–1.5, 1.5–2.5, and 2.5 mm or more.

Statistical analysis

The statistical analysis was performed using SPSS 23.0

Table 1 The PCND and postoperative complications of the published studies

Author	Year	Country	Study design	Case number	Surgical intervention	Complications
Lee (17)	2008	Korea	Retrospective	50	TT + bilateral PCND	4
Lim (18)	2009	Korea	Retrospective	86	TT + bilateral PCND	49
So (19)	2010	Korea	Retrospective	551	TT + bilateral PCND	192
Caliskan (20)	2012	Korea	Retrospective	842	TT/NTT + ipsilateral PCND	179
Park (21)	2014	Korea	Retrospective	193	TT + bilateral PCND or lobectomy plus isthmusectomy + ipsilateral PCND	94
Mao (22)	2015	China	Retrospective	332	TT + ipsilateral or bilateral PCND	81
Chang (23)	2016	Korea	Retrospective	613	Hemithyroidectomy or TT + ipsilateral CLND or bilateral CLND	93
Yu (24)	2017	China	Retrospective	917	Hemithyroidectomy plus prophylactic ipsilateral CLND or TT plus a bilateral CLNM	187
Gui (25)	2018	China	Retrospective	648	Lobectomy plus ipsilateral CLND or TT plus bilateral CLND	141
Luo (26)	2019	China	Retrospective	1,031	Ipsilateral lobe and isthmus resection or TT + ipsilateral CLND or bilateral CLND	41

TT, total thyroidectomy; PCND, prophylactic central lymph node dissection; NTT, not total thyroidectomy (less than total thyroidectomy); CLND, central lymph node dissection; CLNM, central lymph node metastasis.

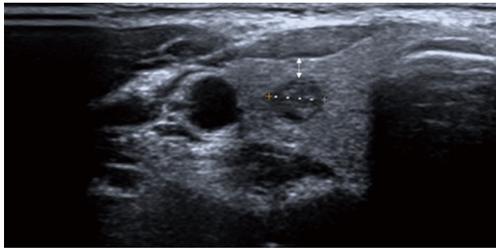


Figure 1 Measurement of distance between tumor to capsule (double headed arrow).

(IBM Corp., Armonk, NY, USA). All significance tests were two-sided. $P < 0.05$ was considered statistically significant. The CLNM was the dependent variable, with the negative converted to 0 and the positive converted to 1. The univariate analysis with the χ^2 -test was used to analyze the statistical correlation between the factors and CLNM. The multivariate logistic regression analysis was performed to find the multivariate correlation of the CLNM. The results were presented in odds ratio (OR) with a 95% confidence interval (CI) and a P value. The nomogram for predicting the CLNM was developed based on gender, age, capsular invasion, and tumor volume. The predictive value of the model was measured using the area under the receiver operating characteristic (ROC) curve. Rstudio was

used to construct a nomogram to predict the CLNM and calibration plot based on gender, age, tumor volume, and capsular invasion.

Results

Patients characteristics

From January 2016 to October 2018, 1,622 patients with PTMC, who underwent surgical treatment at Zhejiang Cancer Hospital, were retrospectively assessed (Table 2). The mean age of these patients was 44.5 ± 10.8 years old, which ranged between 17–80 years old. The mean diameter of the tumor was 5.1 ± 1.6 mm, the mean maximum diameter of the tumor was 5.8 ± 3.2 mm, the mean tumor volume was 92.5 ± 83.7 mm³, and 930 cases had a capsular invasion. For the remaining 692 cases with noninvasive capsules, the mean distance from the capsule was 2.0 ± 1.2 mm, which ranged from 0.5 to 9.7 mm.

Univariate and multivariate analysis

For the univariate multivariable analysis, age ≤ 45 years old ($P < 0.001$), male gender ($P < 0.001$), a larger mean diameter (≤ 5 vs. > 5 mm, $P < 0.001$), a larger maximum diameter (≤ 5 vs. > 5 mm, $P < 0.001$), a larger tumor volume (≤ 90 vs. > 90 mm³,

Table 2 Clinicopathological characteristics of the study patients

Clinical pathological factors	Number of cases (%)
Age (years)	
≤45	846 (52.2)
>45	776 (47.8)
Gender	
Male	362 (22.3)
Female	1,260 (77.7)
Mean diameter (mm)	
≤5	786(48.5)
>5	836 (51.5)
Maximum diameter (mm)	
≤5	568 (35.0)
>5	1,054 (65.0)
Tumor volume (mm ³)	
≤90	944 (58.2)
>90	678 (41.8)
Capsule invasion	
No invasion	692 (42.7)
Invasion	930 (57.3)
Distance from the capsule	
≤1 mm	128 (18.5)
1.0–1.5 mm	161 (23.3)
1.5–2.5 mm	228 (32.9)
>2.5 mm	175 (25.3)

$P < 0.001$), and capsular invasion ($P = 0.011$) were significantly associated with the CLNM (Table 3). For the case of patients without capsular invasion, the tumor distance from the capsule was not statistically significant ($P > 0.05$).

For all cases, each factor was included in a two-class logistic regression multivariate analysis (Table 4). The dependent variable was CLNM, and the independent variables were age, gender, average tumor diameter, tumor volume, and capsular invasion. The risk of CLNM for an average diameter of >5 mm is 1.967 times of that for a diameter of ≤ 5 mm. The risk of CLNM resulted in tumor >5 mm is 2.060 times of tumor ≤ 5 mm. A tumor volume of >90 mm³ was 1.90 times of tumor volumes of ≤ 90 mm³. The risk of CLNM with capsular invasion was 1.391 times of

that of noninvasive capsules. The tumor size and distances from the capsule on the ultrasonography are presented in Figure 2. The distance was not statistically significant in patients without capsular invasion.

Nomogram creation

The nomogram was created with the predictive variables from the statistical analysis. The $\text{Logit}(P) = -0.461 + 0.903 \times \text{gender}$ (when the gender was male) $- 0.036 \times \text{age} + 0.159 \times$ (if with capsular invasion) $+ 0.004 \times$ tumor volume (mm³) was determined, and the predicted probability $\left(P = \frac{e^{\text{Logit}(P)}}{1 + e^{\text{Logit}(P)}} \right)$ was obtained. Based on this, the ROC curve was drawn (Figure 3). The area under the ROC curve was 0.687. According to the corresponding sensitivity and specificity of each point, calculate the point with the maximum value of (sensitivity + specificity-1) as cut off value. A cut-off point for the Prediction of the CLNM was defined as 0.208. The sensitivity was 65.4%, while the specificity was 63.3%. On the basis of multi factor regression analysis, multiple prediction indexes are integrated to get the nomogram (Figure 4). And we verified the prediction ability of the prediction model by internal verification (Figure 5). From these, it could be concluded that the combination of gender, age, capsular invasion, and tumor volume has a certain predictive value for CLNM.

Discussion

Controversy still exists on whether PTMC surgery requires PCND. Therefore, searching for predictors of CLNM in PTMC has great significance for the choice of PCND. At present, there is a consensus on the predictability of gender, age, the maximum diameter of the tumor, and capsular invasion for the CLNM of PTMC (26,28-33). The result of the present study was consistent with this. Additionally, the present study included the average diameter, tumor volume, and distance from the capsule.

Tumor size is presently considered a predictor of CLNM. Most studies have taken the largest diameter of the tumor as the tumor size. Some studies have suggested that tumors >8.5 mm are more aggressive and have a worse prognosis (34). Some studies have suggested that the critical value of PTMC invasiveness could be considered as 7 mm (35). There is no definitive conclusion at present. Furthermore, there are few studies on the predictive significance of approximate tumor volume for CLNM. The

Table 3 Univariate analysis of the clinical pathological factors for central lymph node metastasis

Clinical pathological factors	Number of cases (%)	Central lymph node metastasis (%)		P value
		Positive (n=373)	Negative (n=1,281)	
Age (years)				
≤45	846 (52.2)	234 (64.8)	612 (48.5)	<0.001
>45	776 (47.8)	127 (35.2)	649 (51.5)	
Gender				
Male	362 (22.3)	130 (36.0)	232 (18.4)	<0.001
Female	1,260 (77.7)	231 (64.0)	1,029 (81.6)	
Mean diameter (mm)				
≤5	786(48.5)	128 (35.5)	658 (52.2)	<0.001
>5	836 (51.5)	233 (64.5)	603 (47.8)	
Maximum diameter (mm)				
≤5	568 (35.0)	82 (22.7)	486 (38.5)	<0.001
>5	1,054 (65.0)	279 (77.3)	775 (61.5)	
Tumor volume (mm ³)				
≤90	944(58.2)	165 (45.7)	779(61.8)	<0.001
>90	678 (41.8)	196 (54.3)	482 (38.2)	
Capsular invasion				
No invasion	692 (42.7)	133 (36.8)	559 (44.3)	0.011
Invasion	930 (57.3)	228 (63.2)	702 (55.7)	
Distance from the capsule				
≤1 mm	128 (18.5)	18 (13.5)	110 (19.7)	0.337
1.0–1.5 mm	161 (23.3)	30 (22.6)	131 (23.4)	
1.5–2.5 mm	228 (32.9)	50 (37.6)	178 (31.8)	
>2.5 mm	175 (25.3)	35 (26.3)	140 (25.0)	

Table 4 Multivariate analysis of the clinical pathological factors for central lymph node metastasis

Variable	Central lymph node metastasis risk		P
	OR	95% CI	
Age	0.512	0.400–0.656	<0.001
Gender	2.546	1.959–3.309	<0.001
Mean diameter	1.967	1.539–2.513	<0.001
Maximum diameter	2.060	1.568–2.708	<0.001
Tumor volume	1.902	1.498–2.414	<0.001
Capsular invasion	1.391	1.068–1.781	0.009
Distance from the capsule	1.098	0.911–1.324	0.325

OR, odds ratio; CI, confidence interval.

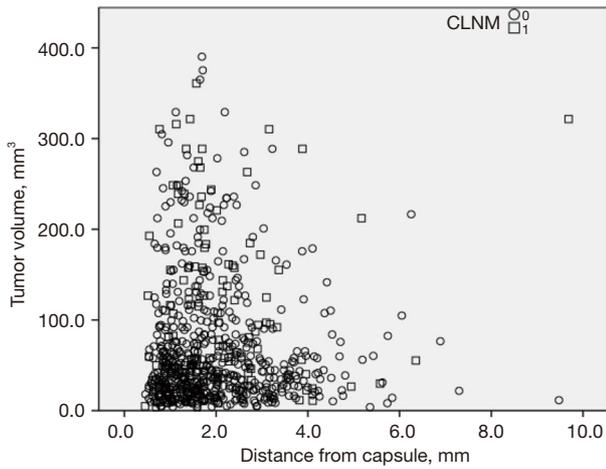


Figure 2 Tumor size and the distance from the capsule on the ultrasonography images. The Pearson correlation was -0.15 . Combined with *Figure 1*, it can be concluded that the correlation between the two is not strong.

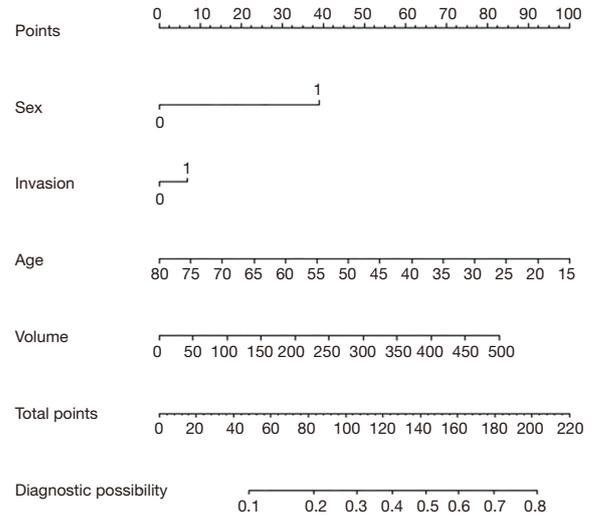


Figure 4 The nomogram to estimate the risk of CLNM based on gender, age, tumor volume, and capsular invasion. CLNM, central lymph node metastasis.

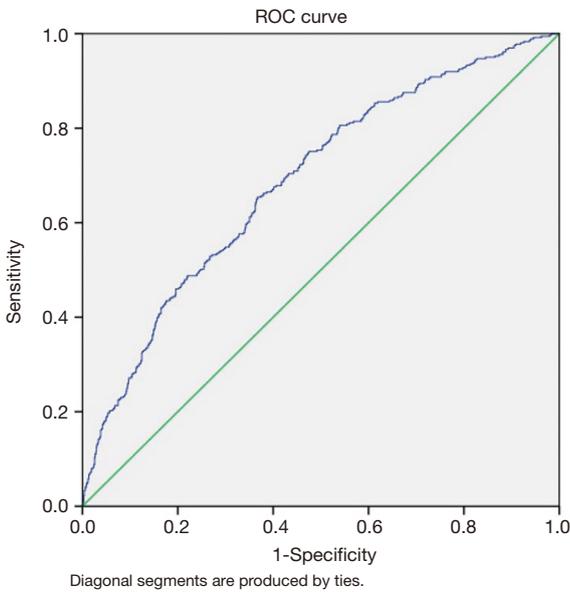


Figure 3 The area under the ROC curve was 0.687. The cut-off points for the Prediction of the CLNM were defined as 0.208. The sensitivity was 65.4%, while the specificity was 63.3%. ROC, receiver operating characteristic; CLNM, central lymph node metastasis.

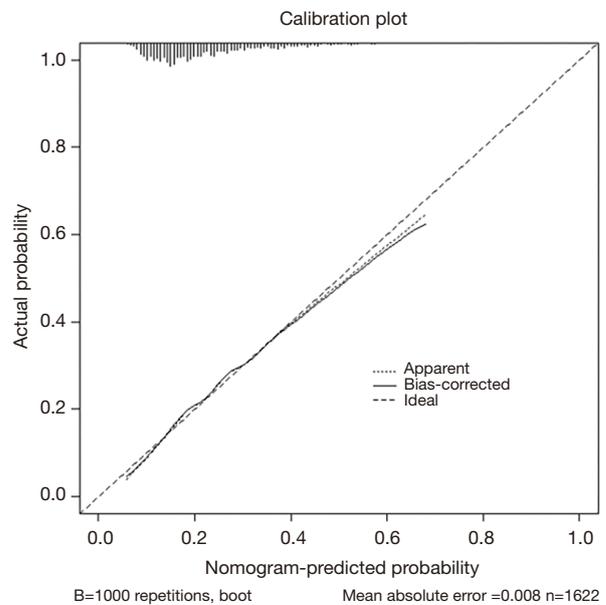


Figure 5 The calibration plot for predicting the performance of the nomogram in estimating the risk of CLNM. When the nomogram-predicted probability was lower than 0.4, the ideal value was close to the actual value. When the nomogram-predicted probability was higher than 0.4, the ideal value is higher. CLNM, central lymph node metastasis.

current study was based on the predictive tumor size for CLNM, and the volume of the tumor was determined using the mean tumor diameter measured on ultrasonography. Considering the tumor as the sphere to obtain the approximate volume, although there was a certain amount of error, this can still be used as a supplementary reference index for the maximum diameter, in order to reduce the possible error. A study revealed that the tumor volume on ultrasonography is a predictor of central neck metastasis of PTC (36). Some studies used the largest tumor diameter and tumor volume to evaluate the size of PTMC tumors. These studies showed that the tumor volume is more sensitive than the maximum diameter of the tumor during the follow-up time for low-risk PTC and that the tumor size change would be more timely. Some scholars have considered that in PTC, the volume is more accurate than the largest diameter to evaluate the tumor size (37,38). Although our study did not demonstrate that the tumor volume is more sensitive than the maximum tumor diameter in the prediction of CLNM (39), the data analysis indicated that tumor volume is a predictor of CLNM. The combination of volume and maximum diameter can more fully and accurately describe the tumor size, and guide for determining whether to perform PCND. In combining these two, the tumor size can be more fully and accurately expressed.

The nomogram revealed that it has predictive performance. The predicted probability can be calculated by combining age, gender, capsular invasion, and tumor volume. Although the sensitivity and specificity were not high, this can be a reference factor for PCND.

The relationship between the thyroid capsule and CLNM has been the focus of many scholars. Most scholars have studied the predictability of capsular invasion for CLNM, and have a common understanding that capsular invasion is a predictor of CLNM (26,29-33). Most scholars have the common understanding that tumor capsular invasion can predict the CLNM of thyroid cancer. Furthermore, some scholars even consider that determining whether the tumor in contact with the capsule more than 25% is predictive of CLNM of PTMC (40,41). Also, some scholars have also studied extracapsular extension, which refers to the extrathyroid extension, or even when the tumor destroys the thyroid capsule, it is considered to be an independent influencing factor of CLNM (25,42,43). However, there are few studies on the correlation of the distance from the capsule for CLNM. Some scholars have selected more than 1 cm of PTC in their investigations

and selected the shortest distance from the capsule on ultrasonography. It has been considered that the distance has a specific significance for predicting the CLNM of PTC. Furthermore, it has been considered that both univariate multivariable analysis and chi-square (χ^2) showed a distance from the capsule <1.9 mm is an important index for the non-metastasis of CLNM ($P < 0.05$) (27). Some scholars had similar conclusions, using spearman correlation analysis, the shorter distance from tumor to capsule, the greater risk in developing of CLNM (spearman correlation coefficient = -0.22, $P < 0.0001$) (44). It is worth mentioning that the former included PTC patients with tumor of 1–3 cm, while the latter included PTC patients with tumor of 0.1–5.6 cm, and the distance ≥ 0 . These are the differences from our study. And when choosing the low-risk PTMC which can be followed up instead of surgery, the PTMC whose tumor is close to the capsule or trachea is excluded. These make us suspect that distance may be a risk factor for CLNM in PTMC patients. However the present study revealed that the distance between the tumor and capsule has no significant predictive value for the CLNM of PTMC. Therefore, as far as the result of the present study is concerned, the distance between the tumor and capsule is not a guiding factor for determining whether PTMC needs PCND.

Scholars have proposed the theory of low-risk PTMC, and have considered that it can be followed up for an extended period, instead of immediately operating. Furthermore, some scholars have proposed a risk stratification for patients who are considered for active monitoring. Some factors include the location of the tumor and an ideal follow-up population. For example, it is surrounded by ≥ 2 mm of normal thyroid parenchyma. The subcapsular position is appropriate; the position is not adjacent to the recurrent laryngeal nerve, without evidence of extrathyroidal extension. Likewise, it is not inappropriate; subcapsular locations are adjacent to the recurrent laryngeal nerve. These result in evidence of extrathyroid extension or clinical evidence of invasion to the recurrent laryngeal nerve or trachea (45). Low-risk PTMC is also mentioned in the 2016 Chinese expert consensus and guidelines for the diagnosis and treatment of PTC, and it was considered that low-risk PTMC could be followed should satisfy the condition that the tumor is not close to the capsule (9). However, indeed, no study has determined whether the distance between the capsule and tumor within the thyroid gland is a high-risk factor. The result of the present study suggests that when the tumor of the PTMC does not invade the capsule, the closest distance from the

tumor to the capsule has no association with the CLNM. Therefore, when screening for low-risk PTMC, it should be considered whether the tumor invades the capsule. If there is no invasion, it would not be meaningful to determine whether the tumor is close to the capsule. China has not yet conducted a long-term follow-up of low-risk PTMC. According to the results of the present study, the follow-up range for low-risk PTMC can be appropriately expanded. This means that more patients can be followed-up with instead of undergoing surgery.

It is worth noting some of the limitations of the present study. First, it can be observed in *Figure 2* that although there were 692 cases of PTMC with tumors within the gland selected in the present study, most of which were small in size and had a short distance from the capsule. Hence, it may not be possible to explore the relevance of distance to CLNM in more detail. Second, although 692 cases of PTMC without capsule invasion were selected for the present study, there was a certain amount of error in the measurement on the ultrasonography image. It can be observed that the closest distance in the present study was 0.5 mm, and there was a possibility that the closer distance (<0.5 mm) was classified as a capsular invasion. However, ultrasonography is an essential method for PTMC, and it is also the most effective and accurate method for measuring the distance between the tumor and capsule. Another limitation is that the present study verified the correlation between tumor volume and CLNM but did not compare tumor volume to the maximum diameter, which is more predictive of CLNM.

In conclusion, the present retrospective study proved that gender, age, maximum diameter, mean diameter, tumor volume, and capsular invasion are predictors of CLNM. When there is no capsular invasion, the distance between the tumor and capsule did not correlate to CLNM. Low-risk PTMC does not need to consider whether the tumor is close to the capsule.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/gs-20-478>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and was approved by Medical Ethics Committee of Zhejiang Cancer Hospital (approval ID: IRB-2020-89). Informed consent was obtained in all cases for the study.

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