

# Preoperative High-Resolution Ultrasound for the Assessment of Macro-Metastatic Central Lymph Nodes Sublevel-By-Sublevel in Unilateral Papillary Thyroid Microcarcinoma

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## Research article

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# Abstract

**Background** To understand the diagnostic efficacy of preoperative high-resolution ultrasound (HRUS) in the diagnosis of macro-metastatic central lymph node (macro-CLNM), It will help surgeons decide whether to perform prophylactic lymph nodes (LNs) dissection in patients with papillary thyroid microcarcinoma (PTMC).

**Methods** This study analyzed the preoperative ultrasound and postoperative pathological results of central lymph nodes sublevel-by-sublevel of 220 patients with unilateral PTMC. These patients all underwent surgery at the Sun Yat-sen University Cancer Center from January 2015 to November 2019.

**Results** In the right paratracheal, the left paratracheal, the pretracheal, and the prelaryngeal level, the mean number of lymph nodes are 0.9, 1.9, 3.3, and 4.6, respectively, and the macro-metastasis rate are 0.91%, 6.36%, 6.73%, and 11.21%, respectively. For metastasis central lymph nodes (CLNM), the HRUS diagnostic efficacy in the four sublevels was low, with the AUC of 0.50-0.54. When the diagnosis object was changed from CLNM to macro-CLNM, the AUC of the ipsilateral paratracheal sublevel has been significantly improved, with 0.80 (95% CI 0.71-0.87) on the left and 0.75 (95% CI 0.67-0.83) on the right. Meanwhile, the negative predictive value (NPV) of ultrasound diagnosis of macrometastasis in ipsilateral paratracheal sublevel reached 99% and 95%.

**Conclusions** The number and macro-metastasis rate of lymph nodes in PTMC patients are, from high to low, the right paratracheal, the left paratracheal, the pretracheal, and the prelaryngeal level. Preoperative HRUS has a high diagnostic efficiency for macro-CLNM in the ipsilateral paratracheal area; when the ultrasound diagnosis of the ipsilateral paratracheal area is negative, the probability of macrometastasis is extremely low.

## Introduction

The global incidence rate of thyroid cancer has increased rapidly by 3–15 times since the 1980s. Among them, the incidence rate of large papillary thyroid cancer (PTC) and other pathological types of thyroid cancer has remained the same compared with that before 1980. The vast majority of rapidly increasing cases are small papillary thyroid carcinoma (less than 15mm), half of which are papillary thyroid microcarcinoma (PTMC)<sup>1, 2</sup>, defined as the longest diameter less than 10mm, regardless of whether there is lymph node metastasis<sup>3</sup>.

Generally, PTMC progresses slowly and has a good prognosis, but it is more often accompanied by central lymph node metastasis (CLNM)<sup>4-7</sup>, which is also proved to be an independent risk factor for recurrence in patients with thyroid cancer<sup>8-11</sup>. The 2015 ATA guideline suggested<sup>12</sup> that thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2), noninvasive, clinically node-negative PTC (cN0) (Strong Recommendation). However, according to the guideline, the patients with thyroid cancer accompanied by macro-metastatic cervical lymph nodes (the cancer foci in

the lymph node longer than 2mm<sup>13</sup>) have an intermediate risk of recurrence. It means that, it is necessary to perform central neck dissection even for PTMC patients if preoperative high-resolution ultrasound (HRUS) detects macro-metastatic central lymph nodes (macro-CLNM). Otherwise, there will be an increasing rate for the second surgery. Therefore, understanding the diagnostic efficacy of preoperative HRUS in the diagnosis of macro-CLNM will help surgeons decide whether to perform prophylactic lymph nodes (LNs) dissection in patients with PTMC. Although several studies indicate that preoperative ultrasound has low diagnostic efficiency for CLNM of PTMC<sup>5, 14</sup>, whether the diagnostic efficacy of HRUS for macro-CLNM is also very low, there has not been any literature report as far as we know.

American Joint Committee on Cancer staging system<sup>15</sup> (AJCC, 8th edition) divides central lymph nodes (LNs) into four sublevels, including prelaryngeal LNs, pretracheal LNs, the left and the right paratracheal LNs. The dissection scope of central LNs for PTMC consisted of the LNs in prelaryngeal, pretracheal, and at least ipsilateral paratracheal sublevel<sup>16</sup>. Although it is difficult to correspond the cervical LNs detected by HRUS with that in pathology one by one, if the central compartment can be subdivided, and the LNs can be corresponded in ultrasonic examinations and pathology according to the four sublevels, the evaluation of HRUS diagnostic efficacy will be more accuracy.

To sum up, this study covered 220 consecutive PTMC patients, comparing their preoperative ultrasound and postoperative pathology of the central LNs in each sublevel to figure out the macro-CLNM rates and the diagnostic efficacy of preoperative ultrasound in each sublevel. It will be a reference for developing individualized surgical plans for PTMC patients.

## Methods

This study was approved by our Institutional Review Board, and the requirement for informed consent was waived because of its retrospective nature. This article's authenticity was validated by uploading the key raw data onto the Research Data Deposit public platform ([www.researchdata.org.cn](http://www.researchdata.org.cn)), with the Research Data Deposit number RDDA2020001813.

## Patients

In order to reduce the interference of the contralateral central lymph node and lateral cervical lymph node metastasis on the analysis of the ultrasound diagnosis performance in each sublevel, this study analyzed the preoperative ultrasound and postoperative pathological results of 220 patients with unilateral PTMC. These patients all underwent surgery at the Sun Yat-sen University Cancer Center from January 2015 to November 2019. The inclusion criteria are as follows: 1) PTMC Patients whose lymph nodes were non-palpable by physical examination; 2) Unilateral PTMC was confirmed by postoperative pathology; the surgery method was thyroidectomy total or lobectomy and ipsilateral central lymph node dissection; 3) preoperative HRUS examination and postoperative pathological results were reported sublevel-by-sublevel. Patients were excluded if they met the following criteria: have received treatment before, with

contralateral central or lateral cervical lymph node dissection, with distant metastases, were followed-up for less than one year, recurrence was found during the follow-up, had incomplete pathological data.

## Preoperative ultrasound examination and diagnosis

Patients included in this study underwent ultrasound examinations one week before the surgery, using a high-resolution sonography system (GE, Mindray, SIEMENS, Toshiba, Super Sonic, Hitachi, PHILIPS, etc.) equipped with an at least 10MHz linear array transducer. Central compartment (level VI) lymph nodes were divided into prelaryngeal, pretracheal, and ipsilateral paratracheal sublevel by AJCC (8th edition). During the preoperative ultrasound examination, the largest and/or the most suspicious LNs detected in each sublevel should be marked down, and the following sonographic features of lymph nodes should be described: the length of the long and short axis, the shape (oval, round, or irregular), the margin (regular or irregular), corticomedullary demarcations (clear or unclear), hilar structure (detected or not detected) and blood flow signals (hilar, peripheral, or mixed type). Besides, for suspicious LNs, the features supporting the diagnosis of metastasis should be recorded. The 2015 ATA guidelines<sup>12</sup> pointed out that the cervical LNs should be considered metastatic if the following sonographic features occurred: round shape, microcalcifications, cystic aspect, hyperechogenicity, and peripheral vascularization.

## Surgery and pathological data

All patients included in this study underwent unilateral central compartment lymph nodes dissection, and the surgical area covered from prelaryngeal level, pretracheal level to ipsilateral paratracheal level, and the excised lymph nodes were marked by sublevels and sent for pathological examination. By reviewing the pathological slices, two experienced pathologists divided the central LNs in each sublevel into no, micro (the cancer foci was shorter than 2mm), and macro-CLNM (the cancer foci was 2mm or longer than 2mm) according to the classification of metastatic LNs in the 8th AJCC<sup>13</sup>. In this study: ☐ a sublevel was defined as no-metastasis sublevel when there were no metastatic LNs; ☐ a sublevel was defined as micro-metastasis sublevel when there was one or more micro-metastatic LNs without any macro-metastatic LNs; ☐ a sublevel was defined as macro-metastasis sublevel when there was at least one macro-metastatic LN. If the two pathologists had different opinions on the diagnosis of the LNs, the two will give a consensus diagnosis after consultation.

## Statistical analysis

We used MedCalc® statistical software to analyze the statistics. The independent-samples t-test was used to compare continuous variables. Categorical variables were compared using the Chi-squared ( $\chi^2$ ) test. We calculated the ultrasound diagnostic accuracy (ACC), sensitivity (SENS), specificity (SPEC), positive predictive value (PPV), negative predictive value (NPV), and the area under the ROC curve (AUC) to find out the ultrasound diagnostic efficacy for macro-CLNM or CLNM in each sublevel. P-values < 0.05 were considered indicative of a statistically significant difference.

## Results

Among the 220 patients with PTMC included in this study, 217 cases were pathologically confirmed as classical variants, while 3 cases were follicular variants. There were 95 patients with metastatic central compartment LNs, which accounted for about 43%. The included cases were divided into 220 sublevels of prelaryngeal LNs, 220 sublevels of pretracheal LNs, 104 sublevels of left paratracheal LNs, and 116 sublevels of right paratracheal LNs (Table 1).

Table 1  
Patient demographics and clinicopathological variables (n = 220)

Characteristics	Total enrolled patients
Age	
≥55y	27 (12.27%)
<55y	193 (87.73%)
Sex	
Male	59 (26.82%)
Female	161 (73.18%)
Hashimoto's thyroiditis	
Yes	30 (13.64%)
No	190 (86.36%)
Number of thyroid lesion	
Single focal	193 (87.73%)
Multifocality	27 (12.27%)
Pathological subtype	
Classical type	217 (98.64%)
Follicular subtype	3 (1.36%)
Thyroid lesions involves the capsule	
Yes	140 (63.64%)
No	80 (36.36%)
Lymph node dissection region	
Left central compartment	104 (47.27%)
Right central compartment	116 (52.73%)

# The number of LNs and macro-metastasis rate in each sublevel according to pathological results

The postoperative pathological results (Table 2 and Table 3) showed a tiny number of prelaryngeal LNs, with only 188 LNs removed in 220 patients. Meanwhile, the LN macro-metastasis rate in prelaryngeal sublevel was also the lowest among all sublevels, only about 0.91%. Next was the pretracheal LNs, with an average number of about  $1.9 \pm 0.1$  LNs per case; the macro-metastasis rate in the pretracheal sublevel was higher than that of the prelaryngeal LNs, reaching 6.36%. It was worth mentioning that the number of LNs in the right paratracheal was significantly beyond that in the left ( $P < 0.0001$ ), whose average values were  $4.6 \pm 0.3$  and  $3.3 \pm 0.2$ , respectively. The macro-metastasis rate of the right paratracheal LNs was also higher than that of the left side, accounting for approximately 11.21% and 6.73%, respectively.

Table 2  
The average number of central lymph nodes sublevel-by-sublevel on pathology in PTMC

	Total number of lymph nodes	Average number of lymph nodes
Prelaryngeal LNs (n = 220)	188	$0.9 \pm 0.1$
Pretracheal LNs (n = 220)	417	$1.9 \pm 0.1$
Left paratracheal LNs (n = 104)	339	$3.3 \pm 0.2$
Right paratracheal LNs (n = 116)	533	$4.6 \pm 0.3$
PTMC, Papillary thyroid microcarcinoma; LNs, Lymph nodes.		

Table 3  
The rate of no-CLNM, micro-CLNM, and macro-CLNM in each sublevel.

	The sublevel of central compartment without macro-metastasis		The sublevel of central compartment with
	no-metastasis	micro-metastasis	macro-metastasis
Prelaryngeal LNs (n = 220)	93.64% (206)	5.45% (12)	0.91% (2)
Pretracheal LNs (n = 220)	82.27% (181)	11.36% (25)	6.36% (14)
Left paratracheal LNs (n = 104)	69.23% (72)	24.04% (25)	6.73% (7)
Right paratracheal LNs (n = 116)	63.79% (74)	25.00% (29)	11.21% (13)

*The size and the HRUS detective rate of macro-metastatic LNs in each sublevel.*

As shown in the Table 4, among the 660 sublevels, the detective rate was extremely low (0–21%) in the prelaryngeal and pretracheal sublevels no matter there was metastatic LNs or not. However, as for ipsilateral paratracheal sublevels, the detective rate of macro-CLNM was higher than non-macro-CLNM, with the macro-CLNM detective rate in left and right paratracheal of 85.71% and 76.92%, respectively, the non-macro-CLNM detective rate of 38.14% and 32.04%, respectively. However, there was no statistical significance in the HRUS detective rate of no- and micro-CLNM in the left and right paratracheal sublevels. In Table 5, the mean long-axis diameter of the macro-CLNM in the prelaryngeal, pretracheal, left paratracheal, and right paratracheal was 4mm, 5.4mm, 4.3mm, and 4.9mm, respectively; the mean long-axis diameter of the non-macro-CLNM was 3mm, 3.5mm, 3.6mm, and 3.1mm, respectively. the long and short-axis diameters of the macro-CLNM were longer than that of the non-macro-CLNM in each sublevel, and there was statistical significance in the pretracheal and left paratracheal sublevels ( $P < 0.05$ ).

Table 4  
The ultrasonic detecting rate of lymph nodes in each sublevel.

	The sublevel of central compartment without macro-metastasis		The sublevel of central compartment with	<i>P-value</i>
	no-metastasis	micro-metastasis	macro-metastasis	
Prelaryngeal LNs (n = 220)	1.46% (3/206)	0% (0/12)	0% (0/2)	–
Pretracheal LNs (n = 220)	7.18% (13/181)	8% (2/25)	21.43% (3/14)	0.003
Left paratracheal LNs (n = 104)	40.28% (29/72)	32% (8/25)	85.71% (6/7)	0.539
Right paratracheal LNs (n = 116)	32.43% (24/74)	31.03% (9/29)	76.92% (10/13)	0.850
The total (n = 660)	12.95% (69/533)	20.88% (19/91)	52.78% (19/36)	0.000
P value: Compare the difference in ultrasound detection rate of lymph nodes with macrometastasis and non-macrometastasis in the sublevel.				

Table 5  
The size of central lymph nodes on pathology in each sublevel.

	Long diameter of LNs		<i>P-value</i>	Short diameter of LNs		<i>P-value</i>
	Non-macro-metastasis (mm)	Macro-metastasis (mm)		Non-macro-metastasis (mm)	Macro-metastasis (mm)	
Prelaryngeal LNs (n = 220)	3 ± 0.4	4	-	2.1 ± 0.3	2.8 ± 0.4	0.523
Pretracheal LNs (n = 220)	3.5 ± 0.3	5.4 ± 0.5	0.000	2.2 ± 0.2	4.3 ± 0.5	0.000
Left paratracheal LNs (n = 104)	3.6 ± 0.3	4.3 ± 0.7	0.004	2.3 ± 0.2	3 ± 0.4	0.333
Right paratracheal LNs (n = 116)	3.1 ± 0.3	4.9 ± 0.4	0.688	1.9 ± 0.2	3.5 ± 0.3	0.317

## The ultrasound diagnostic efficacy for macro-CLNM or CLNM in each sublevel

As revealed in Table 6 and Table 7, no matter for macro-CLNM or CLNM, the HRUS diagnostic efficacy in the prelaryngeal and pretracheal sublevels was low, with the AUC of 0.51 (95% CI 0.44–0.58) and 0.55 (95% CI 0.48–0.62), respectively. Moreover, the false-negative rate of diagnosing prelaryngeal and pretracheal LNs by HRUS reached 100% (2/2) and 86% (12/14), respectively. Among them (Table 4), the proportion of LNs that were not detected by ultrasound was very high, 100% (2/2), 92% (11/12), respectively. Compared with the prelaryngeal-pretracheal sublevels, HRUS was more effective in diagnosing macro-CLNM in the paratracheal sublevels, with the AUC of 0.80 (95% CI 0.71–0.87) in the left and 0.75 (95% CI 0.67–0.83) in the right. Meanwhile, the diagnostic efficacy of macro-CLNM was also significantly higher than that of CLNM in the paratracheal sublevels (0.51 on the left and 0.54 on the right). When the diagnosis object was changed from CLNM to macro-CLNM, the negative predictive value (NPV) was also increased considerably. The NPV of the ultrasound diagnosis of macro-CLNM was 99% of the left paratracheal and 95% of the right side of the paratracheal.

Table 6

Comparison of ultrasonic diagnostic efficiency for LNs macro-metastasis or metastasis in each sublevel

		ACC	SEN	SPE	PPV	NPV	AUC (95% CI)	<i>P</i>
Pre-laryngeal LNs	<b>macro-metastasis</b>	98%	0%	99%	0%	99%	0.51(0.44–0.58)	<i>0.082</i>
	<b>metastasis</b>	92%	0%	99%	0%	94%	0.51(0.44–0.58)	<i>0.082</i>
Pretracheal LNs	<b>macro-metastasis</b>	91%	14%	96%	20%	94%	0.55(0.48–0.62)	<i>0.288</i>
	<b>metastasis</b>	80%	5%	96%	20%	82%	0.50(0.44–0.57)	<i>0.856</i>
Left paratracheal LNs	<b>macro-metastasis</b>	75%	86%	74%	19%	99%	<b>0.80(0.71–0.87)</b>	0.000
	<b>metastasis</b>	59%	31%	71%	32%	70%	0.51(0.41–0.61)	<i>0.834</i>
Right paratracheal LNs	<b>macro-metastasis</b>	80%	69%	82%	32%	95%	<b>0.75(0.67–0.83)</b>	0.000
	<b>metastasis</b>	60%	29%	78%	43%	66%	0.54(0.44–0.63)	<i>0.416</i>
ACC, Accuracy; SEN, Sensitivity; SPE, Specificity;								
PPV, Positive predict value; NPV, Negative predictive value.								
AUC, Area under the ROC curve; CI, Confidence interval.								

Table 7

Comparison between ultrasonography and pathology for central LNs sublevel-by- sublevel in PTMC

		Pathology (a)		Pathology (b)	
		+	-	+	-
<b>Prelaryngeal LNs (n = 220)</b>					
+	0	3	0	3	
-	2	215	14	203	
<b>Pretracheal LNs (n = 220)</b>					
+	2	8	2	8	
-	12	198	37	173	
<b>Left paratracheal LNs (n = 104)</b>					
+	6	25	10	21	
-	1	72	22	51	
<b>Right paratracheal LNs (n = 116)</b>					
+	9	19	12	16	
-	4	84	30	58	
Pathology (a): Macrometastatic lymph node (the length of cancer foci > 2mm) is recorded as pathologically positive;					
Pathology (b): Metastasis lymph node is recorded as pathologically positive.					

## Discussion

Whether patients with PTMC should routinely undergo prophylactic central neck dissection (PCND) remains controversial<sup>17</sup>. On the one hand, some scholars believe that PCND can help reduce recurrence risk and avoid secondary operations complications<sup>18</sup>. What's more, it can help stage the tumor more accurately, which is beneficial for making postoperative supplementary treatment plans (such as I-131 treatment)<sup>19</sup>. On the other hand, there is no definite evidence to prove that PCND can improve the prognosis or prolong the survival of patients with thyroid cancer, and the expansion of the dissection scope will increase the incidence of postoperative complications<sup>19,20</sup>. Lymph node macro-metastasis is a vital risk stratification factor for PTMC patients according to the 2015 ATA guidelines<sup>12,21,22</sup>. Therefore, preoperative identification of macro-CLNM can provide a certain reference for the management of PTMC patients.

The number and macro-metastasis rate of lymph nodes in PTMC patients are, from high to low, the right paratracheal, the left paratracheal, the pretracheal, and the prelaryngeal level. The right paratracheal level has more LNs and a higher macro-metastasis rate than the left side, which may relate to anatomy. The angle between the right RLN and the carotid artery is larger than the angle on the left side, where the RLN is parallel to the tracheoesophageal sulcus<sup>23</sup>.

This study demonstrated that the preoperative ultrasound had an extremely high false-negative rate for assessing macro-metastatic LNs in prelaryngeal-pretracheal sublevel, there were 14 macro-CLNM cases in pretracheal and prelaryngeal sublevel which were diagnosed as negative by HRUS. Among them, HRUS failed to detect any LN in 13 cases. The LNs cannot be observed by ultrasound because the prelaryngeal-pretracheal LNs are located between the anterior cervical muscles and the trachea. The relatively small space in this area makes the number and the size of lymph nodes small. There were only 1–2 prelaryngeal-pretracheal LNs per patient (Table 2); the average short-axis diameter of the prelaryngeal and pretracheal LNs was less than 3mm and 2-4mm, respectively (Table 5), and even the smallest nodule detected by HRUS is only 2-3mm<sup>24</sup>. The extremely low detective rate of HRUS in prelaryngeal-pretracheal LNs caused many false-negative cases, with the AUC of only 0.51–0.55 (Table 6). We suggested that preoperative HRUS did not help identify the macro-CLNM in prelaryngeal-pretracheal sublevel.

Compared with the prelaryngeal-pretracheal sublevel, dissection of LNs in the paratracheal levels is more likely to cause complications such as hoarseness and hypocalcemia common in post thyroid cancer operation because of the injury of recurrent laryngeal nerve and parathyroid<sup>19</sup>. Therefore, the preoperative diagnosis of the paratracheal LNs is of great significance. The diagnostic efficacy of HRUS for CLNM in paratracheal sublevels is low, with the AUC of only 0.51–0.54, which is consistent with the conclusions of other previous studies<sup>5, 14</sup>. For macro-CLNM, the AUC of the paratracheal sublevels has been significantly improved, with 0.80 on the left and 0.75 on the right. This is probably because the diameter of macro-CLNM is larger than that of the non-macro-CLNM (including no- and micro-CLNM) (Table 5), which is more easily to be detected by HRUS (Table 4). In addition, micro-CLNM has only pathological changes below 2 mm, which is difficult to distinguish by ultrasound, while cancer foci in macro-CLNM are larger than 2 mm, which are more likely to show abnormalities in ultrasound images. Moreover, the NPV of ultrasound diagnosis of macrometastasis in paratracheal sublevels reached 99% (left) and 95% (right). In other words, when the paratracheal sublevel is negative under HRUS, the probability of macrometastasis is extremely low, only 1%-5%. Therefore, this study believes that preoperative HRUS has an exclusive diagnostic effect on macrometastasis in paratracheal sublevels.

It is worth mentioning that macrometastasis in prelaryngeal-pretracheal sublevel is a high risk factor for paratracheal macrometastases, with an OR value of 9.1 (95% CI 2.8–29.2, P = 0.0002), And among the patients with macrometastases in prelaryngeal-pretracheal sublevel, nearly 40% of them accompanied by paratracheal macrometastases (6/15). As a result, macro-CLNM in prelaryngeal-pretracheal sublevel has a certain prompting effect on paratracheal LNs macrometastasis. If PTMC patients are found with prelaryngeal-pretracheal macro-CLNM during surgery, it is necessary to be alert to ipsilateral paratracheal macro-CLNM.

This study creatively analyzed the preoperative ultrasound and postoperative pathological results of patients with PTMC sublevel-by-sublevel, figuring out the number of LNs and macro-metastatic rate in each sublevel and discussing the diagnostic efficacy of ultrasound. Compared with the traditional rough analysis of central LNs, the ultrasound diagnostic performance obtained in this paper is more accurate and closer to the real situation. However, there are some limitations to our study. Firstly, in order to reduce the interference of contralateral central LN and lateral cervical LN to the analysis of ultrasound diagnostic performance in each sublevel, this retrospective study design only focus on unilateral PTMC, so there is an unavoidable selection bias. Secondly, this study can only analyze LNs sublevel-by-sublevel rather than single LN one-to-one. It remains a clinically significant topic that urgently needs research on whether combining with other imaging tests or artificial intelligence can improve diagnosis efficiency.

## Conclusion

1. The number and macro-metastasis rate of lymph nodes in unilateral PTMC patients are, from high to low, the right paratracheal, the left paratracheal, the pretracheal, and the prelaryngeal level.
2. Preoperative HRUS has a high diagnostic efficiency for macro-CLNM in the ipsilateral paratracheal area (AUC is 0.80 on the left and 0.75 on the right, respectively); when the ultrasound diagnosis of the ipsilateral paratracheal area is negative, the probability of macrometastasis is extremely low.

## Abbreviations

PTC

papillary thyroid cancer

PTMC

papillary thyroid microcarcinoma

CLNM

metastasis central lymph node

HRUS

high-resolution ultrasound

LN

lymph nodes

Macro-CLNM

macro-metastatic central lymph node

Micro-CLNM

micro-metastatic central lymph node

no-CLNM

no-metastatic central lymph node

non-macro-CLNM

non-macro-metastatic central lymph node

# Declarations

## Ethics approval and consent to participate

This study was approved by Sun Yat-sen University Cancer Center Institutional Review Board, and the requirement for informed consent was waived because of its retrospective nature.

## Consent for publication

All the patients involved in this study were informed and the agreed that their personal data would be used for publication for the purpose of scientific research.

## Availability of data and materials

This article's authenticity was validated by uploading the key raw data onto the Research Data Deposit public platform ([www.researchdata.org.cn](http://www.researchdata.org.cn)), with the Research Data Deposit number RDDA2020001813.

## Competing interests

Wen Tan, Lingli Xiao, Shiwen Zhang, Haoming Zheng, Sheng Li, Yu Zhang, Ankui Yang, Jianhua Zhou, and Longzhong Liu have no conflicts of commercial interest in the subject of study and the source of any financial or material support to disclose.

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## Authors' contributions

Longzhong Liu contributed substantially to the conception of the work; Longzhong Liu, Jianhua Zhou, Wen Tan, and Lingli Xiao participated in the study design; Wen Tan and Lingli Xiao drafted the work; Longzhong Liu, Wen Tan, and Lingli Xiao revised it; Shiwen Zhang, Yu Zhang, and Haoming Zheng participated in the acquisition of the data of the work and offered statistically analysis; Sheng Li and Yu Zhang offered important comments on the methodology; Ankui Yang and Jianhua Zhou provided critical comments on the work. All the authors had read and approved the final article.

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