

# The effect of the area proportion of the metastatic lesion within the central metastatic lymph node on response to therapy in papillary thyroid carcinoma

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**Abstract.** Lymph node (LN) metastasis has been strongly associated with locoregional recurrence and decreased survival time of patients with papillary thyroid carcinoma (PTC). Although the characteristics of the metastatic LNs (mLN) have been determined, including size, number, micro-metastasis and extra-nodal extension (ENE), further analysis is warranted. The present study introduced a new parameter known as the area proportion of the metastatic lesion within the central mLNs (APmCLN). The objective was to evaluate the impact of the APmCLN on response to therapy in patients with PTC. In total, 355 patients with PTC treated with total thyroidectomy and neck dissection, post-operative radioactive iodine and thyroid-stimulating hormone suppression were retrospectively studied. The patients were classified into two groups: Group A (APmCLN  $\leq$ 75%) and group B (APmCLN  $>$ 75%). The association of various clinicopathological characteristics between these two groups was investigated. Univariate and multivariate analyses were used to evaluate risk factors associated with a non-Excellent response to therapy and recurrence-free survival (RFS). The analysis showed that APmCLN  $>$ 75% was significantly associated with extra-thyroidal extension, clinically apparent nodes (cN1), pathological N1b (pN1b), ENE, greater number and larger size of central mLN and larger size of the central LN metastatic lesion. Furthermore, it was reported that chronic lymphocytic thyroiditis, larger central mLN size and APmCLN  $>$ 75% were independent risk factors for a non-excellent response to therapy. Finally, it was determined that the rate of excellent response to therapy was significantly higher in pathological N1 (pN1) patients with

APmCLN  $\leq$ 75% (108/144, 75.0%) compared with patients with APmCLN  $>$ 75% (27/47, 57.4%) ( $P=0.022$ ). However, there was no significant difference ( $P=0.247$ ) between patients with APmCLN  $\leq$ 75% and pN0 (132/164, 80.5%). RFS was 89.4% in patients with pN1-APmCLN  $>$ 75%, whereas those with pN1-APmCLN  $\leq$ 75% and pN0 did not experience a relapse. Patients with PTC with APmCLN  $>$ 75% should be regarded as high-risk and may require more aggressive treatment and careful follow-up.

## Introduction

Papillary thyroid carcinoma (PTC) is one of the most common endocrine malignancies and has a 10-year survival rate of 90-98% globally (1-4). Risk factors including age ( $>$ 45 years), male sex, larger tumor size and distant metastasis contribute to poor survival based on the Surveillance, Epidemiology and End Results (SEER) database (5). Despite the fact that the number of metastatic lymph nodes (mLNs) has been recognized as a negative prognostic factor, other features of mLNs have yet to be fully understood. Recently, the characteristics of mLNs, in particular, size, extra-nodal extension (ENE) and micro-metastasis ( $<$ 0.2 cm as the largest dimension of the metastatic lesion) were initially proposed by the 2015 updated version of the American Thyroid Association (ATA) guidelines (6-8).

PTC often metastasizes to lymph nodes (LNs), especially in the central neck region, and the size of the metastatic lesion within the LN tends to reflect the degree of disease progression (9,10). However, the status of the metastatic lesion within a mLN varies to a large extent. This may include varying metastatic deposit sizes in different LNs of varying size (8,11). Therefore, it is reasonable to be concerned with not only the metastatic lesion size, but also the location within the LN. To better reflect the disease progression of patients with PTC, the present study proposed a novel parameter: The area proportion of the metastatic lesion within the central mLN (APmCLN).

The post-operative risk of recurrence during follow-up should be estimated dynamically according to the response to therapy re-staging system (2015 version of the ATA guidelines) (7). Previous studies have suggested that the therapeutic response system is closely correlated with prognosis (12-16).

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**Key words:** papillary thyroid carcinoma, area proportion, metastatic lesion, lymph node, response to therapy

The objective of the current study was to evaluate the impact of APmCLN on the response to therapy in patients with PTC.

## Materials and methods

**Patients.** Between January 2013 and December 2015, 562 patients with PTC were enrolled onto the study at the Affiliated Sir Run Run Shaw Hospital (Zhejiang, China), and 355 of those underwent a total thyroidectomy (TT) with ipsilateral or bilateral central neck dissection (CND) (Fig. 1). Inclusion criteria were patients with pathologically diagnosed PTC. Exclusion criteria included no PTC diagnosis, poorly differentiated PTC (diagnostic criteria were based on the consensus Turin proposal) (6), coexisting other malignancies, previous thyroidectomy and no radioactive iodine (RAI) ablation. After surgery, a histological diagnosis of PTC and measurements of mLN were confirmed by two experienced pathologists from the Department of Pathology, who were independent from the present study. Of the 355 patients that met the final selection criteria, 191 and 164 were designated as pN1 and pN0, respectively (Fig. 1) (17). In the conventional Tumor-Node-Metastasis (TNM) staging system established by the Union for International Cancer Control and the American Joint Commission on Cancer (AJCC; 2010, 7th edition), pathologically confirmed lymph node metastasis was defined as pN1, no lymph node metastasis was defined as pN0. The study was approved by The Ethics Committee of the Affiliated Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, and all enrolled patients provided written informed consent.

**Treatment protocol.** In accordance with the 2009 ATA guidelines (6), TT was performed if the patient met one of the following criteria: Bilateral nodularity, extra-thyroidal extension (ETE), tumor diameter >1 cm, multifocal lesions in the affected lobe, regional or distant metastases, a personal history of radiation therapy to the head and neck or a first-degree family history of PTC. Ipsilateral CND was performed routinely for the affected side, regardless of whether the central neck LNs were clinically metastatic. Bilateral CND was performed for patients whose tumor(s) was located in the isthmus or both lobes, or for those with clinical metastasis in the neck LNs. Modified lateral neck dissection (LND), including levels II-IV or together with V, was performed only in patients with clinically evident nodal disease in the lateral neck on preoperative ultrasonography or when the ultrasound-guided fine needle aspiration of a lateral node exhibited positive results. RAI remnant ablation was performed postoperatively in all patients according to the 2009 ATA guidelines (6). Only the LNs from the central area were examined, which were derived from patients who underwent CND with or without LND.

**Histopathological examination.** Tissues with thyroid, tumor(s) and LN(s) were collected from each patient during surgery and were sent immediately to the Department of Pathology. Tissues were fixed in 10% neutral-buffered formalin at 4°C overnight, dehydrated using graded ethanol (100, 95, 75 and 50%) and embedded in paraffin. If the thickness of the LNs was <6 mm, they were embedded entirely in paraffin, cut in half, and then sliced into three 3-4- $\mu$ m pieces. If a LN was >6 mm in thickness, it was selected to be embedded and cut in half. All of the slices were stained with hematoxylin and eosin (H&E)

prior to pathological diagnosis (18). In the event of suspicious micro-metastasis, thyroglobulin (Tg) immunohistochemical (IHC) staining was performed (19,20). For IHC, slides were incubated with a primary monoclonal rabbit anti-Thyroglobulin-antibody (1:300 dilution; Abcam; ab156008) at room temperature for 60 min. Then, the slides were incubated with a secondary anti-rabbit IgG antibody (ImmPress Reagent Kit; MP-7405; peroxidase-conjugated) followed by target detection using DAB plus chromogen for 10 min (Gene Tex; GTX73338). All mLNs in the central neck were observed using light microscopy (magnification, x200-400) and measured by two experienced pathologists using an ocular micrometer, and the mean value of the measurements was recorded. In total, 2,768 central LNs were examined, of which 670 were positive, and the one with the largest size, lesion, or metastatic area was selected as the representative parameter for each patient.

**Definitions.** A new parameter (APmCLN) was identified and defined as the ratio of the metastatic deposit area to the whole mLN area in a cross-section, which was microscopically measured by a cross and divided into four quadrants: i)  $\leq 25\%$  (1 Quadrant occupied by the metastatic lesion), ii) 25-50% (2 quadrants occupied by the metastatic lesion), iii) 50-75% (3 quadrants occupied by the metastatic lesion) and iv) >75% (4 quadrants almost occupied by the metastatic lesion) (Fig. 2). When evaluating independent risk factors for treatment response, there was no statistical significance between group i) and ii)+iii)+iv), groups i)+ii) and iii)+iv). However, differences between groups i) +ii) +iii) and iv) were statistically significant. Therefore, groups i)-iii) were merged into group A and group iv) was merged into group B.

Micro-metastasis was defined as the presence of metastatic deposits within a LN <2 mm in diameter, which is a parameter commonly used in breast cancer and other solid tumors (11). Micro-metastasis has been a proposed modification expressed in the 2015 ATA guidelines as a low-risk parameter (7). Patients presenting with histopathological criteria including diffuse infiltration of the thyroid gland with lymphocytes and other inflammation-related cells were diagnosed with chronic lymphocyte thyroiditis (CLT) (21).

The current definition of 'clinically apparent' LN metastasis (clinical N1 disease; cN1) includes any metastatic LN identified by palpation or imaging either before initial surgery or intraoperatively (8). When suspicious LN appeared at level VI or II-IV, it was defined as cN1a or cN1b, respectively.

**Assessment of treatment response.** The response to the therapy re-staging system has been designed for the follow-up of patients with PTC in the 2015 ATA guidelines. According to biochemical, imaging and cyto-pathological findings, there are four response-to-therapy categories for patients treated with TT and RAI remnant ablation (7). These include: i) Excellent response, ii) biochemical incomplete response, iii) structural incomplete response and iv) indeterminate response. The current study rearranged these into two categories consisting of excellent response and non-excellent response. The latter included biochemical incomplete, structural incomplete and indeterminate responses. According to the ATA guidelines, the recurrence rate for the excellent response group is 1-4%, which is much lower compared with other groups (biochemical

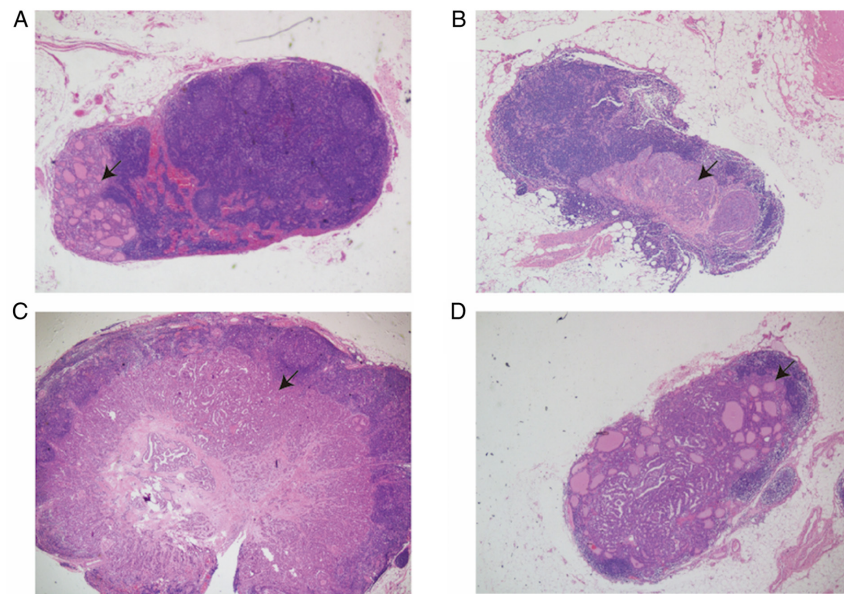


Figure 1. Representative hematoxylin/eosin-stained sections of central metastatic lymph nodes based on the area proportion of these lesions. (A) APmCLN  $\leq 25\%$  (20x magnification). (B) APmCLN  $>25\%$  and  $\leq 50\%$  (40x magnification). (C) APmCLN  $>50\%$  and  $\leq 75\%$  (20x magnification). (D) APmCLN  $>75\%$  (20x magnification). Black arrows indicate the metastatic lesions. APmCLN, area proportion of the metastatic lesion within the central metastatic lymph node.

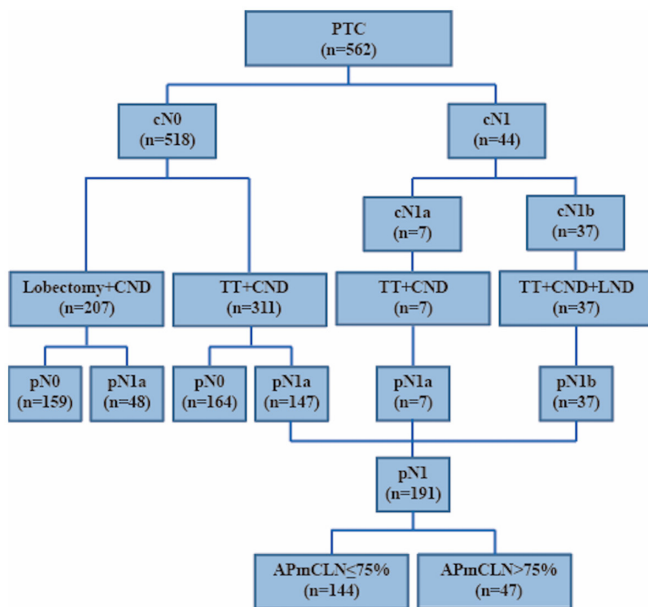


Figure 2. Flow diagram showing the included papillary thyroid carcinoma patients. PTC, papillary thyroid carcinoma; TT, total thyroidectomy; CND, central neck dissection; LND, lateral neck dissection; APmCLN, area proportion of the metastatic lesion within the central metastatic lymph node; c, clinically apparent; N, node; p, pathological.

incomplete response, 20% develop structural disease; structural incomplete response, 50-85% continue to have persistent disease despite additional therapy and indeterminate response, 15-20% will have structural disease) (7).

All patients with PTC were followed up after completion of RAI remnant ablation. Routine neck ultrasound examination, and measurement of serum Tg and anti-thyroglobulin antibody (TgAb) were performed in a state of TSH (Thyroid Stimulating Hormone) suppression every 3 months in the first year and every 6-12 months thereafter. When biochemical or structural

incomplete response occurred, more frequent follow-up was recommended with additional examinations (including CT scan and Fine Needle Aspiration) were proposed. The follow-up time for all PTCs ranged from 40 to 75 months (median, 57 months), and the assessment of response to therapy was based on the latest examination results. Serum Tg (normal range, 1.15-35.00 ng/ml) and TgAb (normal range, 0-4.11 IU/ml) were measured by electrochemiluminescence immunoassay in an Abbott Aeroset® Automated Instrument Analyzer (Canon Medical Systems Corp.) (22-24).

**Statistical analysis.** Continuous variables and categorical variables were determined by Mann-Whitney U test and  $\chi^2$  test (including Fisher's exact tests, if needed), respectively. Bonferroni's correction was also applied where appropriate. The results are presented as medians with range and numbers with percentages. Univariate logistic regression analyses were performed for sex, age, tumor size, tumor multifocality, ETE, CLT, N stage, number and size of central metastatic LN, the size of central metastatic lesion and APmCLN. The variables exhibiting  $P < 0.05$  in the univariate analysis were then selected and analyzed using multivariate logistic regression analysis. The results were represented as odds ratios (ORs) with 95% confidence intervals (CIs). For all analyses, two-sided tests were employed and  $P < 0.05$  was considered to indicate a statistically significant difference. Statistical analyses were performed using SPSS software version 23.0 (IBM Corp.).

## Results

**Characteristics of patients with PTC with TT.** The profiles of 562 patients are shown in Fig. 1. Among them, 207 underwent lobectomy, 355 underwent total thyroidectomy (TT), and these 355 patients included 311 cases of cN0 and 44 cN1. The clinicopathological characteristics of the 355 PTC patients are in Table I. The median age of the cohort was 42 years (range,



13-72 years). Most of the patients were female (77.2%) and were <55 years-old (83.9%). The majority of patients (234/355, 65.9%) were diagnosed with papillary thyroid micro-carcinoma (PTMC, primary tumor size  $\leq 1$  cm). Multifocality, CLT, and ETE were found in 56.1 (199/355), 26.5 (94/355) and 32.4% (115/355) of patients, respectively. The clinical N stage included 311 cN0 (87.6%), 7 cN1a (2.0%) and 37 cN1b (10.4%) patients, whereas the pathological N stage included 164 pN0 (46.2%), 154 pN1a (43.4%) and 37 pN1b (10.4%) patients. An excellent response to primary therapy was observed in 267 patients (75.2%). For ATA risk stratification, there were 157 (44.2%), 100 (28.2%) and 98 (27.6%) patients in low-, intermediate- and high-risk categories, respectively.

*Clinicopathological features associated with the APmCLN of patients with pN1-PTC.* Comparison of the postoperative pathological results revealed several factors that were significantly different between group A (APmCLN  $\leq 75\%$ ) and group B (APmCLN  $>75\%$ ). A larger APmCLN ( $>75\%$ ) was associated with aggressive characteristics, including ETE (P=0.019), clinical node stage (P<0.001) and pathological node stage (P<0.001). To describe the features of the mLNs, a statistical analysis was performed for the number and size of the central mLN and the size and ENE of the metastatic foci. It was demonstrated that these factors were significantly different between the two groups (P=0.001 and P<0.001, respectively). According to the 2015 ATA guidelines, the mLN  $\leq 5$  and micro-metastasis factors belong to the low-risk category. It was reported that these two factors were significantly higher in group A compared with group B (88.2 vs. 63.8% and 71.5 vs. 10.6%, respectively; both P<0.001). Therefore, in group A, the proportion of low- and intermediate-risk categories was 70.1%, whereas in group B, the proportion of intermediate- and high-risk categories was 89.4%. An APmCLN was associated with the risk stratification of disease recurrence (Table II).

*Risk factors for non-excellent response to therapy of patients with pN1-PTC.* Response to initial therapy was analyzed in all patients. The proportion of excellent responders in groups A and B were 75 and 57.4%, respectively. There was a significant difference between the two groups (P=0.022; Table II). The risk factors for non-excellent response to therapy in patients with pN1 PTC were further analyzed (Table III). Univariate analysis indicated that CLT (P<0.001), a higher quantity of central mLN (P=0.004), larger sizes of central mLN (P<0.001) and their metastatic foci (P=0.025) and higher APmCLN (P=0.023) significantly increased the risk of classification into the non-excellent response to therapy category. Furthermore, CLT, size of central mLN and APmCLN were independent variables for response to therapy in multivariate analysis (P<0.00, P=0.014 and P=0.020, respectively). Compared with cases without CLT, those with CLT were 5.405 times (95% CI, 2.339-12.492; P<0.001) more likely to exhibit a non-excellent response to therapy. For cases with an incremental increase of 1 mm in central mLN size, the non-excellent risk increased by 1.283 times (95% CI, 2.339-12.492; P=0.014). For PTCs with APmCLN  $>75\%$ , the rate was 3.917 times higher compared with that of APmCLN  $\leq 75\%$  (95% CI, 1.245-12.327; P=0.020). Therefore, it was demonstrated that APmCLN ( $\leq 75$  vs.  $>75\%$ ) represents a new independent risk factor for predicting clinical outcome.

Table I. Characteristics of 355 patients with papillary thyroid carcinoma who underwent total thyroidectomy.

Characteristics	Total
Sex <sup>a</sup>	
Male	81 (22.8)
Female	274 (77.2)
Age of diagnosis, years	
Median (range), year	42 (13-72)
<55 <sup>a</sup>	298 (83.9)
$\geq 55^a$	57 (16.1)
Primary tumor size, cm <sup>a</sup>	
$\leq 1$	234 (65.9)
$>1$	121 (34.1)
Multifocality <sup>a</sup>	
Absent	156 (43.9)
Present	199 (56.1)
CLT <sup>a</sup>	
Absent	261 (73.5)
Present	94 (26.5)
ETE <sup>a</sup>	
Absent	240 (67.6)
Present	115 (32.4)
Clinical Node stage <sup>a</sup>	
cN0	311 (87.6)
cN1a	7 (2.0)
cN1b	37 (10.4)
Pathological Node stage <sup>a</sup>	
pN0	164 (46.2)
pN1a	154 (43.4)
pN1b	37 (10.4)
Distant metastasis <sup>a</sup>	
Absent	352 (99.2)
Present	3 (0.8)
ATA response-to-therapy category <sup>a</sup>	
Excellent response	267 (72.5)
Biochemical incomplete response	1 (0.3)
Structural incomplete response	15 (4.2)
Indeterminate response	72 (20.3)
ATA risk stratification <sup>a</sup>	
Low	157 (44.2)
Intermediate	100 (28.2)
High	98 (27.6)

<sup>a</sup>Presented as n (%). c, clinically apparent; N, node; p, pathological; ATA, American Thyroid Association; ETE, extra-thyroidal extension; CLT, chronic lymphocyte thyroiditis.

*Effect of the pathological metastasis of central LN on the Response to therapy category.* It was observed that APmCLN affects the response to initial therapy in patients with pN1-PTC. The response to therapy in patients classified as pN0 was further analyzed. A statistically significant difference in excellent

Table II. Characteristics of 191 patients with pN1-papillary thyroid carcinoma according to the APmCLN.

Characteristics	APmCLN		P-value
	Group A $\leq 75\%$ , n=144	Group B $>75\%$ , n=47	
Sex <sup>a</sup>			
Male	37 (25.7)	19 (40.4)	0.054
Female	107 (74.3)	28 (59.6)	
Age of diagnosis, years			
Median (range)	39.5 (20.0-69.0)	37.0 (25.0-66.0)	0.786
$<55^a$	126 (87.5)	44 (93.6)	0.244
$\geq 55^a$	18 (12.5)	3 (6.4)	
Primary tumor size, cm <sup>a</sup>			
$\leq 1$	84 (58.3)	22 (46.8)	0.167
$>1$	60 (41.7)	25 (53.2)	
Multifocality <sup>a</sup>			
Absent	62 (43.1)	21 (44.7)	0.845
Present	82 (56.9)	26 (55.3)	
ETE <sup>a</sup>			
Absent	95 (66.0)	22 (46.8)	0.019
Present	49 (34.0)	25 (53.2)	
CLT <sup>a</sup>			
Absent	108 (75.0)	39 (83.0)	0.259
Present	36 (25.0)	8 (17.0)	
Clinical Node stage <sup>a</sup>			
cN0	123 (85.4)	24 (51.1)	$<0.001$
cN1	21 (14.6)	23 (48.9)	
Pathological Node stage <sup>a</sup>			
pN1a	128 (88.9)	26 (55.3)	$<0.001$
pN1b	16 (11.1)	21 (44.7)	
Number of central mLN			
Median (range)	2.0 (1.0-19.0)	5.0 (1.0-18.0)	$<0.001$
$\leq 5^a$	127 (88.2)	30 (63.8)	$<0.001$
$>5^a$	17(11.8)	17 (36.2)	
Size of central mLN, mm			
Median (range)	4.33 (0.67-14.90)	6.40 (1.07-18.27)	0.001
Size of central LN metastatic foci, mm			
Median (range)	1.34 (0.07-6.80)	5.33 (1.07-18.27)	$<0.001$
$<2^a$	103 (71.5)	5 (10.6)	$<0.001$
$\geq 2^a$	41 (28.5)	42 (89.4)	
ENE <sup>a</sup>			
Absent	135 (93.8)	30 (63.8)	$<0.001$
Present	9 (6.2)	17 (36.2)	
ATA response-to-therapy categories <sup>a</sup>			
Excellent response	108 (75.0)	27 (57.4)	0.022
Non-excellent response	36 (25.0)	20 (42.6)	
ATA risk stratification <sup>a</sup>			
Low	52 (36.1)	5 (10.6)	0.003
Intermediate	49 (34.0)	19 (40.4)	
High	43 (29.9)	23 (49.0)	

<sup>a</sup>Presented as n (%). APmCLN, area proportion of the metastatic lesion within the central metastatic lymph node; CLT, chronic lymphocytic thyroiditis; ETE, extra-thyroidal extension; LN, lymph node; mLN, metastatic lymph node; ENE, extra-nodal extension; ATA, American Thyroid Association; c, clinically apparent; N, node; p, pathological.

Table III. Relationships between clinicopathological variables and non-excellent response-to-therapy in patients with pN1-papillary thyroid carcinoma.

Characteristics	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Sex, male vs. female	1.546 (0.754-3.171)	0.235		
Age of diagnosis, <55 vs. ≥55 years	0.534 (0.171-1.664)	0.279		
Primary tumor size, ≤1 vs. >1 cm	1.116 (0.597-2.087)	0.730		
Multifocality, absent vs. present	1.755 (0.918-3.356)	0.089		
ETE, absent vs. present	0.833 (0.437-1.590)	0.580		
CLT, absent vs. present	6.462 (3.114-13.413)	<0.001	5.405 (2.339-12.492)	<0.001
Pathological N stage, pN1a vs. pN1b	1.623 (0.764-3.447)	0.207		
Clinical N stage, cN0 vs. cN1	1.529 (0.749-3.120)	0.244		
Number of central mLN, ≤5 vs. >5	3.026 (1.410-6.493)	0.004	2.082 (0.821-5.280)	0.123
Size of central mLN, mm	1.216 (1.103-1.341)	<0.001	1.283 (1.051-1.566)	0.014
Size of central LN metastatic foci, mm	1.110 (1.013-1.215)	0.025	0.823 (0.652-1.039)	0.102
APmCLN, ≤25 vs. >25%	1.148 (0.610-2.158)	0.669		
APmCLN, ≤50 vs. >50%	1.826 (0.973-3.428)	0.061		
APmCLN, ≤75 vs. >75%	2.222 (1.114-4.432)	0.023	3.917 (1.245-12.327)	0.020
ENE, absent vs. present	1.083 (0.441-2.659)	0.861		

APmCLN, area proportion of the metastatic lesion within the central metastatic lymph node; CLT, chronic lymphocytic thyroiditis; ETE, extra-thyroidal extension; LN, lymph node; mLN, metastatic lymph node; c, clinically apparent; N, node; p, pathological.

Table IV. Response to therapy categories on the pathological metastasis of central lymph node of patients with papillary thyroid carcinoma treated with total thyroidectomy.

Characteristics	ATA response-to-therapy categories, n (%)		P-value
	Excellent	Non-Excellent	
pN0	132 (80.5)	32 (19.5)	0.247 <sup>a</sup>
pN1-APmCLN ≤75%	108 (75.0)	36 (25.0)	0.022 <sup>b</sup>
pN1-APmCLN >75%	27 (57.4)	20 (42.6)	

<sup>a</sup> $\chi^2$  test for pN0 vs. APmCLN <75% of pN1; <sup>b</sup> $\chi^2$  test for APmCLN ≤75% vs. APmCLN >75% of pN1. APmCLN, area proportion of the metastatic lesion within the central metastatic lymph node.

response to therapy was observed between patients in the APmCLN ≤75% and APmCLN >75% (P=0.022) categories, after using Bonferroni's correction, it still passed the statistical significance (P=0.022 <0.050/2). The excellent response to therapy rates were 75 and 57.4%, respectively. Notably, when comparing the pN0 and pN1-APmCLN ≤75% groups, there was no statistical difference in the rate of achieving an excellent response to treatment (P=0.247), and the incidence rates for these two groups were 80.5 and 75.0%, respectively (Table IV). Therefore, it is reasonable to believe that APmCLN >75% will make response to therapy worse than APmCLN ≤75%.

*Recurrence-free survival (RFS) according to the APmCLN.* In total, five cases of disease recurrence were identified during the median follow-up period of 57 months (range, 40-75 months) across all patients with PTC who underwent

TT. The mean time of recurrence was 25.8 months. According to the APmCLN, the number of recurrence cases was higher in the pN1-APmCLN >75% group compared with the pN1-APmCLN ≤75% group (5/47 vs. 0/144, respectively), and the RFS was also significantly different between the two groups (89.4 vs. 100%; log-rank P<0.001). In addition, RFS of the pN1-APmCLN ≤75% and pN0 patients were both 100% and no patients relapsed (Fig. 3). Therefore, pN1-APmCLN >75% indicates a higher recurrence rate in PTC patients.

## Discussion

PTC is generally an indolent disease that has an excellent prognosis. The SEER registry study concluded that the overall survival rate at 14 years is 82% in cases of PTC without LN metastases and 79% with nodal metastases in America (25).

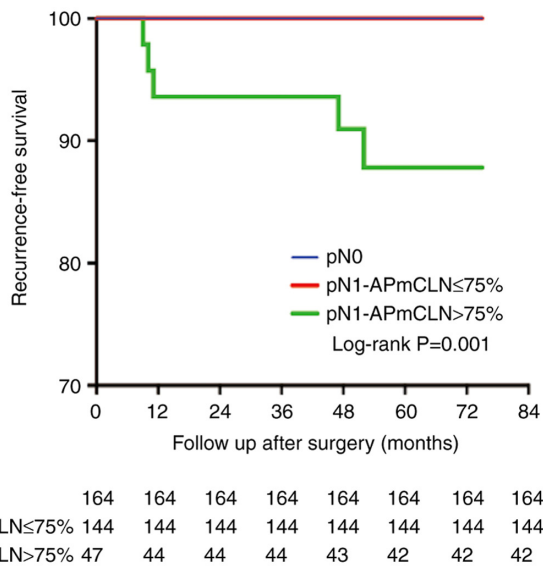


Figure 3. Kaplan-Meier curves showing recurrence-free survival according to the APmCLN. APmCLN, area proportion of the metastatic lesion within the central metastatic lymph node; N, node; p, pathological.

Therefore, an understanding of which patients require long-term follow-up for assessing disease status is needed. Methods to reduce the risk of recurrence and disease-specific death is also important. Previous studies have shown that the evaluation of clinical outcome in patients with PTC should be dynamically adjusted throughout the observation period (26-29). A key step in risk re-evaluation is to assess the response to primary therapy and analyze the clinical data obtained from imaging, biochemical and cytopathological examination during dynamic monitoring, especially within the first 2 years of follow-up (7,15). According to the ATA guidelines, the response to therapy re-classification describes differences in clinical status and outcomes at various points during the observed progress period (7). For example, one study demonstrated a recurrence rate of 1-4% in the excellent response group, while for the remaining three groups, the likelihood of disease recurrence, persistence or progression is significantly increased (7).

The weight of LN metastasis has been decreased in the assessment of the new TNM system in patients with PTC. The nodal status does not affect TNM staging in patients <55 years old. In patients >55 years old with T1 or T2, N1 can promote the stage from I to II (17). However, LN metastasis in the central neck occurs frequently in PTC (10) and correlates with locoregional recurrence (8,30). Therefore, for the assessment of recurrent risk according to the 2015 ATA guidelines, the extent of LN involvement, including the number and size of mLN and LN metastasis, was added and emphasized (7). In previous years, some researchers have been concerned with the impact of other mLN parameters on PTC biological behavior and prognosis, such as ENE (31), cancerous nodules of LNs (32) and the ratio of metastatic LNs to total LNs removed (33,34). In the present study, APmCLN was initially introduced as a new parameter and its effect on PTC prognosis was analyzed.

Although five mLNs in cN0, micro-metastasis and the central mLN (mCLN) size were added to the 2015 ATA

guidelines as new factors of recurrence risk assessment, the two parameters were not found to affect the response of initial treatment in the current study. The risk factors of non-excellent response to therapy were also evaluated using univariate and multivariate analyses. The presence of CLT, larger size mCLN and APmCLN >75% were independent risk factors for non-excellent response to therapy in patients with PTC with pN1.

There is no definitive conclusion as to whether CLT is linked with a particular set of clinicopathological characteristics or prognosis in PTC. Some studies have shown that multifocality and LN metastasis occurs more frequently in patients with CLT (35-37). In contrast, other studies found associations between the presence of CLT and improved features, such as smaller tumor size, less advanced TNM stage, lower frequency of LN metastasis and improved prognosis (38-40). In the present study, CLT was recognized as a risk factor for non-excellent response to therapy in PTC. One of the characteristics of CLT is abnormally elevated TgAb that does not return to normal within 2 years in some patients after TT (41-43). The increased TgAb may interfere with the measurement of Tg, which would affect evaluation of the initial treatment response (44-46). Therefore, it was hypothesized that CLT may not be suitable for predicting treatment response.

The size of the mCLN is an important prognostic factor for patients with PTC, and larger mCLNs tend to be more aggressive. Ito *et al* (47) showed that the presence of mLN >1.5 cm is associated with a significantly lower disease-free survival rate compared with patients with either N0 disease or patients with pN1 disease <1.5 cm. Similarly, Sugitani *et al* (48) reported that in patients with pN1 disease with the largest mLN (>3 cm, 27%), the risk of recurrence within 10 years after TT and neck dissection without RAI ablation was significantly higher compared with pN1 patients (<3 cm, 11%). In the present study, larger-sized central mLN was significantly associated with an increased risk of non-excellent response to therapy. However, because of the long-term stimulation of inflammation, the central LNs of CLT are relatively larger. Therefore, it may be unreasonable to consider the larger mCLN size as an independent risk factor for poor treatment response if the inference factor of CLT is not ruled out.

To better reflect the metastatic extent of LNs, the present study put forward the novel parameter of APmCLN, which includes two factors. These are the size of the metastatic LN and its metastatic foci, and whether the influence of inflammation due to CLT may be ruled out. This was conducted so that the definition of APmCLN is more scientific and rational. Previous studies have reported that the sizes of mLN and LN metastasis are indicators of tumor aggressiveness and risk factors for prognosis in PTC (47,49-51). However, coexisting CLT, the frequently changing size of mCLN changes and the size of mLN foci were not independent risk factors for non-excellent response to therapy in the current study. It is inaccurate to predict treatment response based only on CLT and the size of mLNs, therefore the present study included APmCLN and systematically analyzed its clinicopathological and prognostic value in patients with pN1-PTC after TT and CND. APmCLN >75% exhibited worse clinicopathological features, a poor prognosis and may be regarded as



a new independent risk factor for non-excellent response to therapy. Therefore, there was sufficient data to conclude that APmCLN may be a reliable and practical new indicator for predicting response to therapy and prognosis in patients with pN1-PTC.

Several limitations were evident in the current study. First, there were only 355 patients enrolled and only five relapsed cases were reported in the relatively short follow-up period. Therefore, additional studies with longer follow-up times and multicenter data are needed. Second, APmCLN is currently a categorical variable. The 75% critical value is obtained through step classification and comparison between groups. If it is a continuous variable, the cut-off value can be calculated using an ROC curve (52-54), which is more scientific. Given the differences in the color and cell morphology of H&E-stained sections between tumor and normal tissue, software, such as ImageJ and ITK-SNAP (55-58), can be used to identify the boundary, obtain the location and range of metastases in the LN, and calculate the area proportion of the metastatic lesion. This more extensive analysis would allow APmCLN to be analyzed as a continuous variable. Third, according to the ATA guidelines (2015 version) (7), some patients with PTMC are recommend Active Surveillance rather than surgery. Active Surveillance is applying life-long diagnostic modalities to evaluate changes in disease status without treatment, until progression of the disease becomes clinically apparent (59-61). Regular follow-up should be provided for the patient to ensure that disease progression is tolerable without any additional therapeutic options, such as surgery. However, due to the retrospective nature of the present study, most of the patients enrolled had undergone surgical treatment, which was inconsistent with the current ATA guidelines (7). The present patients were recruited between 2013 and 2015, and treated according to the 2009 ATA guidelines (6) and the Chinese Thyroid Association (62) in which thyroid surgery is recommended if the lesion is considered to be malignant.

In conclusion, APmCLN >75% was an indicator of tumor aggressiveness and a significant independent risk factor for non-excellent response to therapy in patients with pN1-PTC. These results may enable physicians to further stratify patients into various risk groups and develop effective individual follow-up and treatment plans.

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### Availability of data and materials

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

### Authors' contributions

LHS and LeX designed the study and confirm the authenticity and legitimacy of all raw data. LHS wrote the manuscript. LZ, JW and LJ performed the data collection and analysis. LHS interpreted the results. YL performed the histological examination, and confirmed the diagnosis. LiX performed the follow-up plan and collected the data from patients. LeX supervised the project. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

This study was approved by The Ethics Committee of the Affiliated Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (Hangzhou, China). All patients provided written informed consent.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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