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Incorporation size of lymph node metastasis focus and pre-ablation stimulated Tg could more effectively predict clinical outcomes in differentiated thyroid cancer patients without distant metastases

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Background: The size of lymph node metastasis (LNM) and pre-ablation stimulated Tg (ps-Tg) were key predictors of clinical prognosis in differentiated thyroid cancer (DTC) patients, however, very few studies combine the above two as predictors of clinical prognosis of DTC patients.

Methods: Persistent/recurrent disease and clinicopathologic factors were analyzed in 543 DTC patients without distant metastases who underwent LN dissection, near-total/total thyroidectomy, and radioiodine ablation.

Results: In the multivariate analysis, size of LNM, ps-Tg, and the activity of ¹³¹I significantly correlated with long-term remission. The optimal cutoff size of LNM 0.4 cm-1.4 cm (intermediate-risk patients) and >1.4cm (high-risk patients) increased the recurrence risk (hazard ratio [95% CI], 4.674 [2.881-7.583] and 13.653 [8.135-22.913], respectively). Integration of ps-Tg into the reclassification risk stratification showed that ps-Tg ≤ 10.1 ng/mL was relevant to a greatly heightened possibility of long-term remission (92.2%–95.4% in low-risk patients, 67.3%–87.0% in intermediate-risk patients, and 32.3%–57.7% in high-risk patients).

Conclusion: The cutoff of 0.4 cm and 1.4 cm for a definition of size of LNM in DTC patients without distant metastases can reclassify risk assessment, and incorporating ps-Tg could more effectively predict clinical outcomes and modify the postoperative management plan.

KEYWORDS

differentiated thyroid cancer, lymph node metastasis, pre-ablation stimulated Tg, ¹³¹I therapy, prognosis

Introduction

In recent decades, differentiated thyroid cancer (DTC), specially papillary thyroid cancer (PTC), is continually metastasizes to the cervical lymph nodes(LN), the occurrence of lymph node metastases (LNM) in PTC has been reported to range from 31.5% to 50.0% (1–4). Therefore, further attention has been paid to accurate evaluation of the risk stratification in patients with DTC. Recently, the 2015 American Thyroid Association (ATA) Initial Risk Stratification System based on LNM has been proposed for assessing the chance of having poor prognosis during follow-up (5, 6). Nevertheless, based on clinical experience, the size of LNM is commonly distributed between 0.2 cm and 3 cm. Therefore, the 2015 risk stratification system may not precisely predict the clinical prognosis.

The size of LNM is defined as a focus full of thyroid cancer metastases in the LNM with the largest dimension. Emerging literature has demonstrated that the size of LNM is an independent risk factor of persistent/recurrent disease in DTC patients. As the size of LNM increases, it is more significantly associated with poor prognosis (7–15). Recent writing has reported that pre-ablation stimulated Tg (ps-Tg) measured under levothyroxine withdrawal just earlier radioiodine (RAI) ablation is an independent risk factor of persistent/recurrent disease, the ps-Tg (≤ 10.1 $\mu\text{g/L}$) is greatly connected with long-term remission in DTC patients (13, 16).

The size of LNM and ps-Tg were key predictors of clinical prognosis in DTC patients, however, very few studies combine the above two as predictors of clinical prognosis of DTC patients. This research was undertaken to find out the optimum cutoff size of LNM and to incorporate size of LNM and ps-Tg to accurately assess clinical prognosis in patients with DTC.

Materials and methods

Data source

We retrospected the electronic medical records of DTC patients from July 2014 to June 2017 at the Department of Nuclear Medicine

at Zhujiang Hospital, Southern Medical University, after getting of approval by the local Institutional Review Board.

Patients

The patients who underwent cervical LN dissection, near-total/total thyroidectomy and then conduct the first RAI ablation in our hospital (17) were ruled out if they meet the following standards (1): patients had distant metastases upon surgery or in initial RAI ablation, (2) patients had missing data or incomplete data on size of LNM, (3) patients had previous RAI ablation in other hospitals, (4) patients had positive thyroglobulin antibody (TgAb) (> 115 IU/mL), (5) patient follow-up time was < 24 months after the first RAI ablation (Figure 1).

The data was reviewed including patient demographics, surgery, and pathology reports. The pathologic TNM classification was based on the American Joint Commission on Cancer (AJCC), 8th edition.

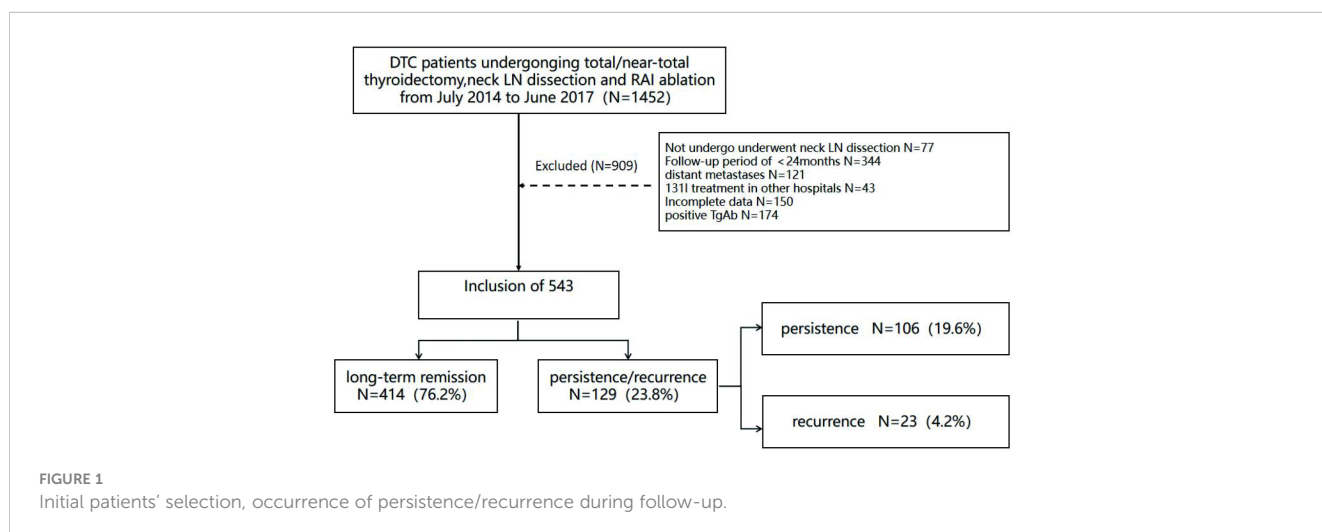
Size of LNM and Tg measurements

The size of LNM is defined as a focus full of thyroid cancer metastases in the LNM with the largest dimension observed in multiple serial sections using microscope. The pathology slides were analyzed and measured the size of metastatic foci in each LN by An experienced pathologist (7).

Roche Cobase 801 electrochemiluminescence instrument was utilized for measurement of Tg (measuring range: 0.04–5000 $\mu\text{g/L}$). All ps-Tg was measured underlevothyroxine withdrawal just earlier RAI ablation in the same laboratory in our hospital.

Treatment and follow-up

Before RAI ablation, patients were informed to obey a low-iodine dietary for 3–4 weeks and levothyroxine withdrawal for 3



weeks; this was prolonged for 1 week if TSH levels did not reach 30 $\mu\text{IU/mL}$. An empiric RAI administered activity was used to decide the activity of ^{131}I , using 1.85–3.70 GBq for thyroid remnant ablation and 3.70–7.40 GBq for postoperative residual cervical LNM.

After the initial RAI ablation, follow up every 3–6 months for the first 2 years. When achieving stable disease, follow up every 6–12 months. Patients were regularly followed-up with *via* measurement of Tg, thyroglobulin antibody (TgAb), and neck ultrasound during thyroid hormone therapy, using the 2009 ATA guidelines (18). Additional imaging methods including ^{18}F -FDG PET/CT, ^{131}I whole-body scans (WBS), chest and mediastinal computed tomography were performed when suppressed Tg (rTG) was $>1 \mu\text{g/L}$ or when suspicious loco-regional/distant metastases were detected.

Incomplete biochemical or structural response within one year of the initial RAI ablation was considered persistence disease. Meanwhile, patients who were earlier considered as having significant effect to therapy was defined as recurrence disease, when they show functional, structural, or biochemical evidence of disease. For the above patients, further treatment plans including repeated surgery, extra RAI therapy, and other therapies were taken by the attending physician.

Clinical outcomes evaluation and definition

A total of data locked in June 2022 were utilized to determine clinical outcomes. At final follow-up, patients were considered to have long-term remission if they had a rTG $< 1 \mu\text{g/L}$, no observable TgAb, and no structurally identifiable evidence. Patients were considered as having persistent/recurrent disease if they had a rTG $> 1 \mu\text{g/L}$, stimulated Tg $> 10 \mu\text{g/L}$, or any evidence of disease on functional imaging (^{18}F -FDG PET/CT, ^{131}I WBS), structural imaging (ultrasonic, CT, or MRI), or biopsy-proven disease. Patients with persistent/recurrent disease were classed as having either structural evidence of disease on imaging or biochemical evidence of disease (rising TgAb, rTG $> 1 \mu\text{g/L}$, or stimulated Tg $> 10 \mu\text{g/L}$ without a structural evidence of disease). And patients with structural evidence of disease were fulfilled the undermentioned standards (1): highly suspicious focus on the neck ultrasound (short axis $> 5 \text{ mm}$, number, rounded shape, irregular margins, loss of the fatty hilum, enlarged cortex, heterogeneous parenchymal echotexture, hypoechoic parenchymal echogenicity, calcifications, cystic change or necrosis, disorganized peripheral vascularity during follow-up), (2) positive cytology/histology, or (3) findings on ^{18}F -FDG PET/CT, ^{131}I WBS, or other imaging highly suspicious of metastatic evidence (11, 13, 16, 19–21). Disease free survival (DFS) was defined as the period of time among the discovery of persistent/recurrent disease and first operation.

Statistical analysis

Statistical analysis was performed using SPSS software (version 26.0). Categorical data were presented as numbers and percentages.

Qualitative parameters were analyzed using chi square test or Fisher's exact test and are expressed as frequencies and percentages. Continuous data were presented as the mean \pm SD or the median (range). A P value < 0.05 was considered statistically significant. The X-tile software was used to acquire the optimum cut-off for the size of LNM to predict persistent/recurrent disease (22). Multivariate analysis was done for variables with a P value < 0.05 in the univariate analysis to determine the statistical risk factors associated with poor prognosis. Curves of DFS were fabricated using the Kaplan-Meier method, and log-rank tests were used to assess the differences in DFS among the risk stratification. Missing data were handled using complete case analysis.

Results

Patient characteristics

Of the 1,452 consecutive DTC patients who underwent near-total/total thyroidectomy administered in our department during the study, 77 patients were excluded because they did not undergo neck LN dissection, 344 patients were excluded because they had < 24 months of follow up, 121 patients were excluded because of distant metastases upon surgery or initial RAI ablation, and 43 patients were excluded because they had received previous ^{131}I treatment at other hospitals. In addition, 150 patients were excluded due to missing data or incomplete data on size of LNM (missing pathology reports: $N = 32$, incomplete data on size of LNM: $N = 118$), and 174 patients were ruled out due to the positive TgAb ($> 115 \text{ IU/mL}$). Finally, 543 patients with DTC were involved in the final cohort (Figure 1).

The median of the primary tumor size was 1.5 cm (range: 0–9.0 cm). Patients with positive LN was 494 (91.0%), with a median number of positive LNs of 5 (range: 0–79). The median size of LNM was 0.4 cm (range: 0–5.0 cm). The median ^{131}I -administered activity was 5.55 GBq (range: 1.85–22.94 GBq). The number of patients with multiple RAI ablation was 101 (18.6%) (Table 1).

Outcomes

The median of follow-up was 63 months (range: 24–122 months). Before initial RAI ablation, 356 patients had no functional or structural evidence of disease and 48 (13.5%) patients had poor prognosis at final follow-up. In addition, 71 patients had highly suspected structural evidence of disease upon ultrasonic examination, and 43 (60.6%) patients had persistent/recurrent disease. Functional evidence of disease was found in 83 patients upon ^{131}I post-therapy WBS, only 16 (19.3%) patients had persistent/recurrent disease, 33 patients had structural and functional evidence of disease, and 22 (66.7%) patients had persistent/recurrent disease.

Further, 442 patients taken one RAI ablation, and 57 (12.9%) patients had poor prognosis. Ninety-two patients taken two RAI ablations, 62 (70.7%) patients had poor prognosis, 9 patients taken three RAI ablations, and 7 (77.8%) patients had poor prognosis.

TABLE 1 Characteristics of the study patients (n = 543).

Characteristics	Value
No. of patients	543
Sex	
Male	191(35.2%)
Female	352(64.8%)
Age at diagnosis (y), median (range)	39(6-76)
<55	481(88.6%)
≥55	62(11.4%)
Extent of lymph node dissection	
Central lymph node dissection	247(45.5%)
Lateral lymph node dissection	19(3.5%)
Central and lateral lymph node dissection	277(51.0%)
Histology	
Classic PTC	519(95.6%)
FV-PTC	9(1.7%)
FTC	5(0.9%)
Aggressive histology	10(1.8%)
Incomplete tumor resection	8(1.5%)
Gross ETE	87(16.0%)
BMI(kg/m2)	
<18.5	52(9.8%)
18.5-24	287(52.9%)
>24	190(35.0%)
Primary tumor size (cm), median (range)	1.5cm(0-9cm)
Bilateral tumor	177(32.6%)
Multifocal tumor	253(46.6%)
Capsular invasion	325(59.9%)
Invasion of loco-regional tissues or structures	133(24.5%)
Vascular invasion	64(11.8%)
Invade nerves	41(7.6%)
Ta	3(0.6%)
T0	329(62.3%)
T1	93(17.6%)
T2	67(12.7%)
T3	34(6.4%)
T4	2(0.4%)
Tx	
Na	48(8.8%)
N0	252(46.4%)
N1a	243(44.8%)
N1b	
Initial risk stratification	
Low risk	64(11.8%)
Intermediate risk	405(74.6%)
High risk	74(13.6%)
BRAFV600E mutation of primary tumor	366(80.8%)
Number of invaded lymph nodes, median (range)	5(0-79)
>5	220(40.1%)
≤5	323(58.9%)
Size of the largest metastatic LN(cm),median (range)	0.4cm(0-5cm)
Extranodal extension of LN	199(46.1%)
Multiple RAI ablation	101(18.6%)

(Continued)

TABLE 1 Continued

Characteristics	Value
Cumulative 131I-administered activities(GBq), median (range)	5.55(1.85-22.94)
<7.40	440(81.0%)
≥7.40	103(19.0%)
Ps-Tg (ng/mL), median (range)	4.47(0.04-1511.20)
<10	360(66.3%)
≥10	183(33.7%)
TSH(μIU/mL), median (range)	63.19(5.26-115.92)
<30	22(4.1%)
≥30	521(95.9%)
TGAb (kU/L), median (range)	14.31(10.00-114.60)
Follow-up information Median follow-up (m), median (range)	63 (24-122)
Last status	
No evidence of disease	414(76.2%)
Persistent structural disease	68(12.5%)
Persistent biomedical disease	16(2.9%)
Recurrent structural disease	38(7.1%)
Recurrent biomedical disease	7(1.3%)

PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; FV-PTC, follicular variant PTC; ps-Tg, pre-ablation stimulated thyroglobulin; LN, lymph node; BMI, Body Mass Index; ETE, extrathyroidal extension. TSH, thyroid stimulating hormone; TGAb, thyroglobulin antibody. aTNM staging was determined by 8th American Joint Cancer Committee Tumor-Node-Metastasis stage system.

Generally, long-term remission was obtained in 414 patients (76.2%). In total 129 patients (23.8%) had poor prognosis, 106 patients (19.6%) had a structural incomplete response, and 23 patients (4.2%) had a biochemical incomplete response. Twenty-one patients with positive cytology/histology underwent repeated surgery, 7 patients (33.3%) had a significant effect, 6 patients (28.6%) changed from structural incomplete response to biochemical incomplete response, 7 patients (33.3%) maintained structural incomplete response, and 1 patient (4.8%) had distant metastases. There were no death associated with DTC during study.

Performance of size of LNM

The median value of the size of LNM was 0.4 cm (range, 0-5.0 cm), with a median value of 0.3 cm in patients with long-term remission and 1.1 cm in patients with poor prognosis (P < 0.001) (Figure 2). The median of time interval among first operation and initial RAI ablation was 2.0 months (range, 0-103 months).

The optimum cut-off value for the size of LNM was decided using the X-tile software (version 3.6.1, Yale University), and the result is shown in Figure 3A. All patients were divided into 3 risk stratification for the assessment of long-term remission. There were 282 patients with the size of LNM ≤ 0.4 cm (low-risk group), 199 patients with the size of LNM ranging from 0.4 cm to 1.4 cm (intermediate-risk group), and 62 patients with the size of LNM > 1.4 cm (high-risk group) (Figure 3B). Curves of DFS were shown in the Kaplan-Meier method, the low-risk group had 92.2% DFS rates, intermediate-risk group had 67.3% DFS rates, high-risk group had 32.3% DFS rates. The hazard ratio (95% CI) of the high-risk patients

and intermediate-risk patients were 13.653 (8.135–22.913) and 4.674 (2.881–7.583), respectively. The low-risk patients was used as the reference (Figure 3C).

Univariate and multivariate analyses of long-term remission

During the univariate analyses, various risk factors were identified to be significantly related to predictors of long-term remission (Table 2). Meanwhile, these risk factors were further included in multivariate analysis. Cumulative 131I-administered activity, the size of LNM and ps-Tg were independent factors in predicting clinical outcome (Table 3).

Integrating the size of LNM with ps-Tg

Recently, some studies report that the ps-Tg cut-off was 10.1 $\mu\text{g/L}$ (13, 16). When we combined the size of LNM with ps-Tg (Figure 4), we found that patients with a ps-Tg $\leq 10.1 \mu\text{g/L}$ had a considerably increased DFS rates (low-risk = 95.4%, intermediate-risk = 87.0%, and high-risk = 57.7%). In contrast, patients with ps-Tg $> 10.1 \mu\text{g/L}$ had a considerably reduced DFS rates in each risk group (92.2–81.0% in low-risk patients, 67.3%–40.5% in

intermediate risk patients, and 32.3%–13.9% in high-risk patients) (Figure 4).

Discussion

In our study, we found that patients with highly suspected structural evidence of disease or both highly suspected structural and functional evidence of disease before initial RAI ablation had poorer long-term remission (39.4% and 33.3%, respectively). In addition, patients with NSD or only functional evidence had excellent long-term remission (86.5% and 80.7%, respectively). Patients with two or more RAI ablations had poorer long-term remission (two ablations = 29.3%, three ablations = 22.2%). Patients with structural evidence of disease had improved clinical outcomes (61.9%) following repeated surgery.

In summary, our data show the prognostic value of the size of LNM for predicting long-term remission. The cutoff of 0.4 cm and 1.4 cm for a definition of LNM in pN1 can reclassify risk assessment. In our cohort, the low-risk group had 92.2% DFS rates, intermediate-risk group had 67.3% DFS rates, high-risk group had 32.3% DFS rates. This held true for all patients who underwent neck LN dissection.

More significantly, this study demonstrated that integration of the size of LNM with ps-Tg more accurately predicted long-term

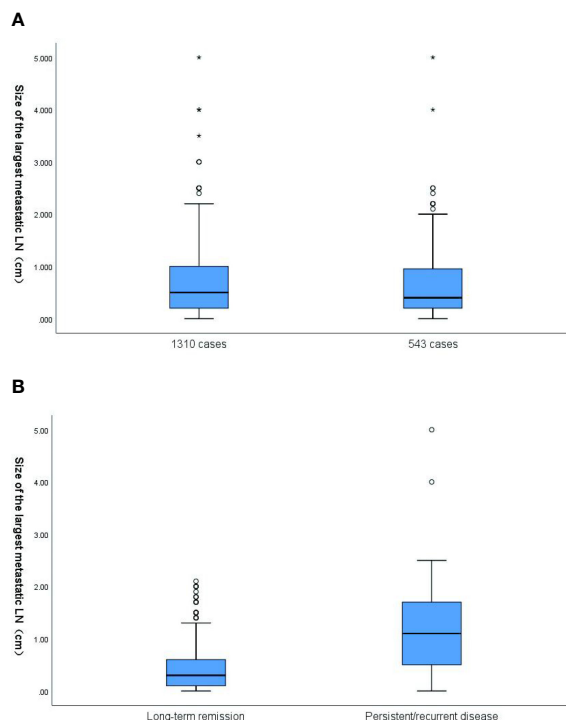


FIGURE 2

(A) Box plot of the distribution of size of the largest metastatic LN in 1310 cases (all patients with size of the largest metastatic LN) and 543 cases (the final cohort consisted of 543 patients). In 1310 cases, the mean value of size of the largest metastatic LN was 0.66cm (range,0-5cm).In 543 cases, the mean value of size of the largest metastatic LN was 0.62cm (range,0-5cm) ($p=0.189$). (B) Box plot of the distribution of size of the largest metastatic LN based on response to the therapy at the end of follow-up. The corresponding median size of the largest metastatic LN was 0.3cm and 1.1cm, respectively, for patients classified as disease free and these with persistent/recurrent disease. The size of the largest metastatic LN results are plotted on a logarithmic scale. LN, lymph node.

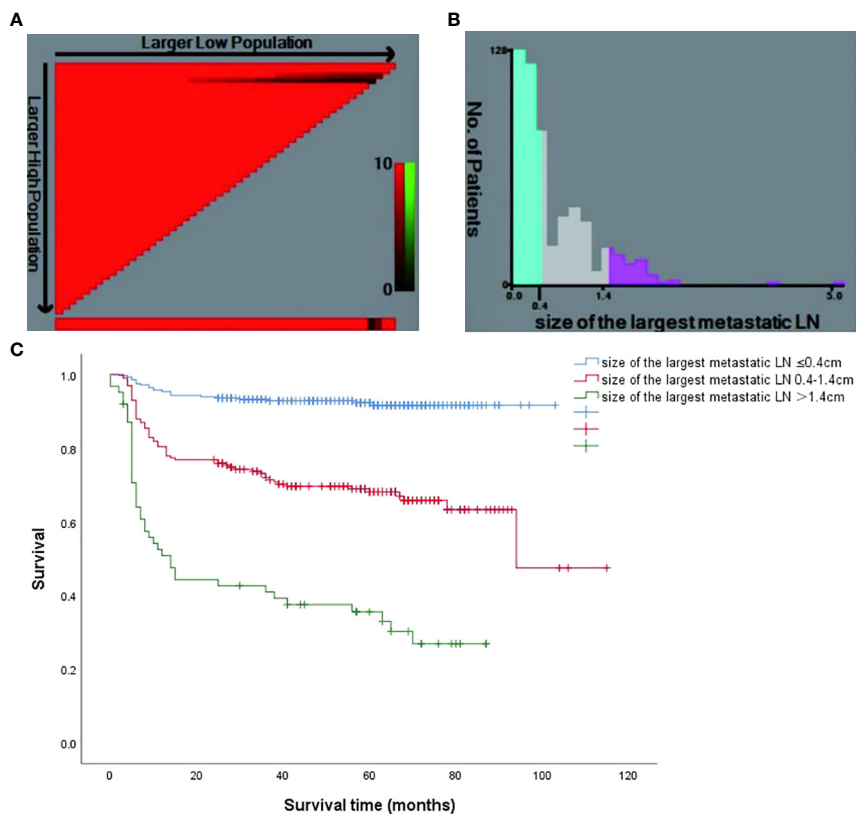


FIGURE 3 (A) The X-tile software of size of the largest metastatic LN for the prediction of persistent/recurrent disease vs long-term remission. (B) Patient frequency according to the size of the largest metastatic LN (the optimal cutoffs were 0.4cm and 1.4cm); (C) Kaplan Meier survival curves for different risk groups ($P < 0.001$).

TABLE 2 Univariate analysis of predictors of persistent/recurrent disease.

Parameters	Long-term remission	Persistence/recurrence	χ^2 or Fisher	P
No. of patients (%)	414	129		
Sex			5.033	0.025
Male	135	56		
Female	279	73		
Age (y)			0.162	0.687
≥55	46	16		
<55	368	113		
Extent of lymph node dissection			27.257	<0.001
Central lymph node dissection	214	33		
Lateral lymph node dissection	12	7		
Central and lateral lymph node dissection	188	89		
Number of surgeries			25.647	<0.001
1	384	99		
2 or moer	30	30		
Histology			14.215	0.003
Classic PTC	398	121		
FV-PTC	8	1		

(Continued)

TABLE 2 Continued

Parameters	Long-term remission	Persistence/recurrence	χ^2 or Fisher	P
FTC	5	0		
Aggressive histology	3	7		
Incomplete tumor resection			0.847	0.357
Yes	5	3		
No	409	126		
Gross ETE			11.491	0.001
Yes	54	33		
No	360	96		
BMI(kg/m ²)			1.321	0.517
<18.5	42	10		
18.5-24	214	73		
>24	148	42		
Primary tumor size (cm)			4.254	0.119
≤2	304	86		
>2	95	41		
X	2	0		
Bilaterality			1.638	0.201
Yes	129	48		
No	285	81		
Multifocality			9.065	0.003
Yes	178	75		
No	236	54		
Capsular invasion			23.948	<0.001
Yes	224	101		
No	190	28		
Invasion of loco-regional tissues or structures			18.619	<0.001
Yes	83	50		
No	331	79		
Vascular invasion			9.383	0.002
Yes	39	25		
No	375	104		
Invade nerves			3.966	0.046
Yes	26	15		
No	386	114		
T			16.990	<0.001
T0T1、T2	339	87		
T3、T4、Tx	62	41		
N			32.818	<0.001
N0	45	3		
N1a	211	41		
N1b	158	85		
ATA risk stratification			28.478	<0.001
Low	62	2		
Intermediate	309	96		
High	43	31		
BRAFV600E mutation of primary tumor			0.291	0.589
Yes	276	90		
No	68	19		
Number of invaded lymph nodes			34.834	<0.001
≤5	275	48		
>5	139	81		
Size of the largest metastatic LN(cm)			114.573	<0.001
≤0.4	260	22		
0.4-1.4	134	65		
>1.4	20	42		

(Continued)

TABLE 2 Continued

Parameters	Long-term remission	Persistence/recurrence	χ^2 or Fisher	P
Extranodal extension of LN			31.493	<0.001
Yes	123	76		
No	199	34		
Cumulative ^{131}I -administered activities(GBq)			162.279	<0.001
≤ 7.40	385	55		
> 7.40	29	74		
ps-Tg (ng/mL)			111.610	<0.001
≤ 10.1	324	36		
> 10.1	90	93		

ATA, American Thyroid Association; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; FV-PTC, follicular variant PTC; ps-Tg, preablation stimulated thyroglobulin; LN, lymph node; BMI, Body Mass Index; ETE, extrathyroidal extension.

TABLE 3 Multivariate analysis of predictors of persistent/recurrent disease.

Parameters	OR(95%)	P
Sex		
Male	1	
Female	0.993(0.531-1.858)	0.982
Extent of lymph node dissection		
Central lymph node dissection	1	
Lateral lymph node dissection	0.649(0.121-3.482)	0.614
Central and lateral lymph node dissection	0.582(0.175-1.935)	0.377
Number of surgeries		
1	1	
2 or more	1.598(0.641-3.983)	0.315
Histology		
Classic PTC	1	
FV-PTC	0.979(0.081-11.846)	0.987
FTC	0	0.999
Aggressive histology	6.217(0.426-90.734)	0.182
Gross ETE		
Yes	1	
No	0.950(0.210-4.292)	0.946
Multifocality		
Yes	1	
No	1.224(0.649-2.308)	0.533
Capsular invasion		
Yes	1	
No	1.165(0.535-2.537)	0.701
Invasion of loco-regional tissues or structures		
Yes	1	
No	1.501(0.679-3.319)	0.316
Vascular invasion		
Yes	1	
No	1.218(0.485-3.058)	0.674
T		
T0, T1, T2	1	
T3, T4, Tx	0.933(0.339-2.571)	0.894
N		
N0		
N1a	2.432(0.738-8.012)	
N1b		0.144
ATA risk stratification		
Low	1	
Intermediate	3.278(0.367-29.235)	0.288
High	3.634(0.237-55.784)	0.354

(Continued)

TABLE 3 Continued

Parameters	OR(95%)	P
Number of invaded lymph nodes		
≤5	1	1
>5	0.760(0.363-1.593)	0.468
Size of the largest metastatic LN(cm)		
≤0.4	1	
0.4-1.4	2.444(1.100-5.432)	0.028
>1.4	6.614(2.204-19.850)	0.001
Extranodal extension of LN		
Yes	1	
No	1.280(0.660-2.485)	0.465
Cumulative 131I-administered activities(GBq)		
≤7.40	1	
>7.40	6.679(3.162-14.109)	<0.001
ps-Tg (ng/mL)		
≤10.1	1	
>10.1	4.646(2.457-8.786)	<0.001

ATA, American Thyroid Association; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; FV-PTC, follicular variant PTC; ps-Tg, pre-ablation stimulated thyroglobulin; LN, lymph node; BMI, Body Mass Index; ETE, extrathyroidal extension.

remission. The ps-Tg ≤ 10.1 µg/L had a greatly increased DFS rates to 95.4%, 87.0%, and 57.7% in the low-, intermediate-, and high-risk patients, respectively. Conversely, the ps-Tg > 10.1 µg/L had a greatly reduced DFS rates for all categories (92.2%–81.0% in low-risk patients, 67.3%–40.5% in intermediate-risk patients, and 32.3%–13.9% in high-risk patients).

Although LNM related to clinical outcomes has been reported previously. For example, in a study including 3,198 TC patients, Zhang et al. (14) found that N stage was associated with poor prognosis. Patients with NX were associated with the worst long-term remission and the highest mortality risk, while patients with pN1 were more possible to occur lung metastasis (48%). In most studies analyzing the size of LNM (cut-off value between 0.2 cm and 3 cm) using the 2015 ATA guidelines, LN micrometastasis (< 0.2 cm) referred to breast cancer and other solid tumors (5, 7, 8, 14, 15, 23). In a study, 16-year follow-up of 233 PTC patients showed that patients with N0 or LN micrometastasis had excellent long-term remission (87.3% and 83.8%, respectively) (10). This is consistent with our findings that patients with N0 and LN micrometastasis had excellent

long-term remission (93.9% and 94.9%, respectively), meanwhile, this study found that a size of LNM ≥ 2 mm was significantly associated with persistent/recurrent disease. Differently, Lee et al. (24) found that the newly proposed definition of LN micrometastasis using a cut-off value of 3.5 mm resulted in reclassification of the risk estimates of structural recurrence. And another study has similar report that the size of LNM (cut-off value of 0.536 cm) was significantly associated with a structural incomplete response (7). In addition, several studies have estimated optimal cut-off values (1.0 cm, 1.5 cm, and 3.0 cm, respectively) for the size of LNM to predict clinical outcomes (8, 12). It should be mentioned that the cut-off values (0.4 cm and 1.4 cm) in our study are close to the above results. Finally, in clinical practice, it is very rare to identify bulky LN metastasis (≥3 cm). In a study of 184 patients, Iglesias et al. identified only four cases (2.2%) of huge LN metastasis, which is consistent with the two cases shown in our data (0.4%) (12). Therefore, size of LNM using 2015 ATA guidelines may lead to the inaccurate prediction of clinical outcomes. Furthermore, Barres et al. and Tian et al. (13, 16) demonstrated that ps-Tg (cut-off value of 10.1 ug/L) had significant

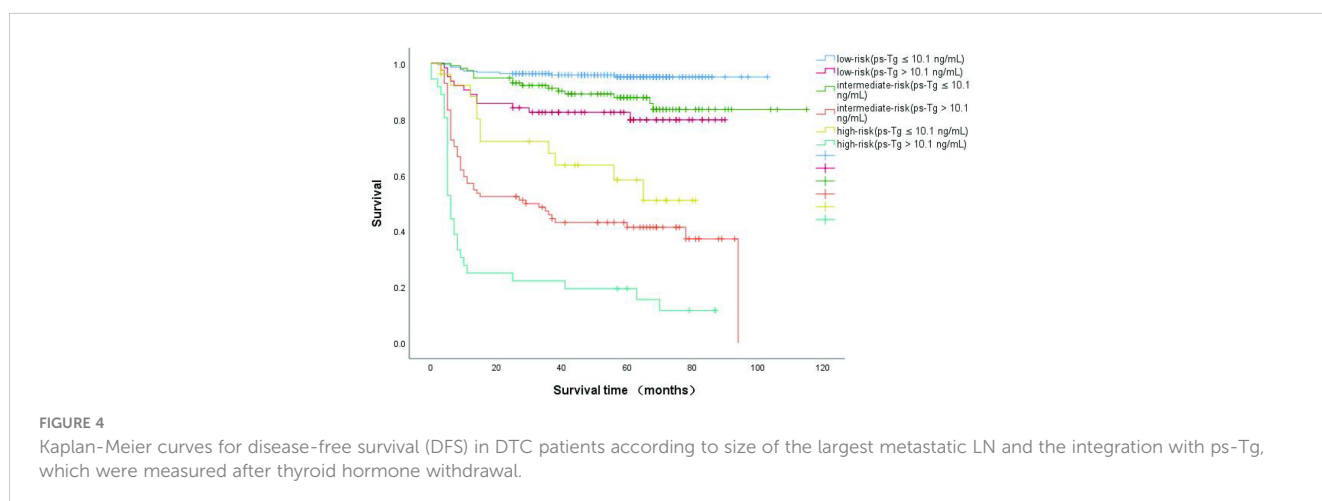


FIGURE 4 Kaplan-Meier curves for disease-free survival (DFS) in DTC patients according to size of the largest metastatic LN and the integration with ps-Tg, which were measured after thyroid hormone withdrawal.

effects on long-term remission in two large studies involving 1,319 and 2,524 patients. Although the impact of the size of LNM on long-term remission has been reported previously, most studies report only one cut-off value. We divided the patients into 3 risk stratification, and, for the first time, combined the size of LNM with ps-Tg to predict long-term remission.

Some patients did not exhibit LN micrometastasis in the neck preoperative, or were diagnosed as low-risk and did not undergo neck LN dissection (25). This may lead to selection bias, and therefore, such patients were not included in this study ($p = 0.13$). Although some studies (8, 9) have suggested that having cN0 or LN micrometastasis may not reduce the overall survival rate, Zhao et al. (26) found that prophylactic central neck dissection reduced regional recurrence. Therefore, it has been suggested in recent years that patients with DTC should be offered more aggressive surgery (5, 25, 27).

The overall DFS rate of 76.2% are coincided with the Statistical data found in some recent research (13, 16, 28, 29). However, our research has some shortages. First, different surgical scope, the retrospective design, and the single-center research design were prone to selection biases. Second, the usefulness of the size of LNM and ps-Tg measurements was researched through post analysis. Furthermore, the size of LNM was measured at our hospital before initial RAI ablation in some patients, which may affect the accuracy of measurement. In addition, only the size of LNM and extranodal extension of LN (some data on extranodal extension of LN were missing) were considered. Therefore, we did not analyze each LN and its distribution. Finally, although a median follow-up period of 63 months is an acceptable start for prediction of long-term remission, longer follow-up are required to evaluate the long-term efficacy. However, it is important to note that recurrence disease was far more rare than persistent disease. This may be due to residual lesions (41.5%) caused by surgery (29–31).

Conclusions

This study suggested the cutoff of 0.4 cm and 1.4 cm for a definition of size of LNM in DTC patients without distant metastases can reclassify risk assessment, and incorporating ps-Tg could more effectively predict clinical outcomes and modify the postoperative management plan.

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Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

JX and WO contributed to the conception and design of the study. JW, XX, XL and CL organized the database and acquired the data. PC and JQW prepared the figures and tables. JL and LP performed the statistical analysis. JX wrote the first draft of the manuscript. WO and HF critically revised the manuscript and supplemented the data for the final draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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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