Predictors of thyroglobulin in the lymph nodes recurrence of papillary thyroid carcinoma undergoing total thyroidectomy

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Research

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Abstract

Purpose: To investigate serum thyroglobulin (Tg) levels in recurrent papillary thyroid carcinoma (PTC) patients, thereby evaluating possible risk factors and structural features of lymph nodes (LNs) recurrence.

Patients and Methods: All the patients with primary PTC who underwent total thyroidectomy (TT) with central or lateral neck dissection and then re-operated due to LNs recurrence between January 2013 and June 2018 were included. Patients were subdivided groups by different Tg levels.

Results: This study included 60 patients with LNs recurrence. Of all, 49 patients underwent radioactive iodine (RAI) treatment. Maximum unstimulated Tg (uTg) ≥ 0.2 ng/mL were associated with larger diameter of recurrent LNs ($P = 0.027$), higher possibility of diameters of recurrent LNs ≥ 25mm ($P = 0.023$) and higher ratio of metastatic LNs ($P < 0.001$). Pre-RAI ablation serum-stimulated Tg (off-Tg) ≥ 1ng/mL and unstimulated Tg detected at 1 week after RAI ablation (on-Tg) ≥ 0.2 ng/mL were associated with larger diameter of recurrent LNs and higher possibility of diameters of recurrent LNs ≥ 25mm. Number of metastatic LNs ≥ 8 was an independent predictor for maximum uTg ≥ 0.2 ng/mL (OR = 8.767; 95% CI =1.392-55.216; $P = 0.021$). Ratio of metastatic LNs ≥ 25% was an independent predictor for off-Tg ≥ 1 ng/mL (OR = 20.997; 95% CI =1.649-267.384; $P = 0.019$).

Conclusion: Tg-positive was associated with larger size of recurrent LNs. Number of metastatic LNs ≥8 could independently predict maximum uTg-positive. Ratio of metastatic LNs ≥ 25% was an independent predicator for off-Tg-positive.

Introduction

Papillary thyroid carcinoma (PTC) accounts for 90% of thyroid cancer pathologies and its incidence is rapidly growing worldwide[1]. PTC is frequently associated with metastasis to lymph nodes (LNs) in the central compartment (level VI) of the neck and then lateral compartment (level II to V)[2]. Total thyroidectomy (TT) with central neck dissection (CND) is often preferred as an initial surgical procedure for patients with thyroid cancer > 4 cm, or with gross extrathyroidal extension, or clinically apparent metastatic disease to nodes, and could also for patients with thyroid cancer > 1 cm and < 4 cm without extrathyroidal extension and without clinical evidence of any LNs metastases[1]. Selective or modified lateral neck dissection (LND) is performed under fine-needle aspiration cytology proven nodal metastasis[3]. Then postoperative radioactive iodine (RAI) is another important treatment modality dependent on the characteristics of the primary tumor and the risk of persistent or recurrent disease[1,4]. Although existing surgery with RAI treatment is expected to be adopted, occasionally risk of recurrence of PTC was unavoidable especially for N1b patients[5].

Serum thyroglobulin (Tg) and anti-thyroglobulin antibody (TgAb) levels are recommended for the assessment of residual or recurrent diseases because the well-differential cancer or thyroid follicular cells is the only source of serum Tg[1]. The serum Tg level is supposed to reach its lowest concentration at 3 to

4 weeks after TT. Therefore, it is useful for detecting persistent or recurrent diseases measuring Tg level from this time point[6]. Studies suggested the potential value of the Pre- RAI serum-stimulated Tg (off-Tg) on predicting recurrent diseases of metastatic PTC other than unstimulated Tg detected at 1 week after RAI ablation (on-Tg), though disputes still existed[7,8].. At the same time, LNs recurrence is the most common form of residual or recurrent diseases apart from distant metastasis and biochemical recurrence, which is detectable under regular ultrasound examination during follow-up[9]. However, the relationships between serum Tg levels and the risk of these LNs recurrence remained unclear. Some studies demonstrated that Tg measurement has the potential to serve as a useful negative predictor of persistent and recurrent PTC[10], while some reported serum Tg levels cannot be considered as reliable indicators for the absence of disease in patients already treated with RAI[11].

Thus, the objective of this study was to investigate Tg levels in recurrent PTC patients, thereby evaluating probable risk factors and structural features of LNs recurrence to help guide clinicians in selecting optimal therapy and postoperative surveillance.

Methods

Patients

We reviewed our clinical database containing 901 consecutive records of patients with PTC. All the patients with primary PTC who underwent TT and then re-operation due to LNs recurrence in the Department of Thyroid & Parathyroid Surgery, West China Hospital, Sichuan University between January 2013 and June 2018 were included retrospectively. All surgeries were performed by an experienced surgeon team. All recurrent LNs were confirmed by postoperative pathology. Neoplasms were grouped into stages according to the American Joint Committee for Cancer (AJCC) staging system (8th edition)[12]. Exclusive criteria included (1) Patients did not undergo re-operation. (2) Parathyroid surgery, subtotal thyroidectomy. (3) Incomplete data. This study was approved by the medical ethics committee of West China Hospital, Sichuan University.

Treatments And Follow-up

Primary surgery for patients was TT. Then prophylactic CND (ipsilateral or bilateral) was routinely performed in patients with clinically uninvolved central neck LNs. Therapeutic CND (level VI) was conducted in patients with pathologically involved central LNs. For patients with lateral LNs metastases diagnosed at preoperative ultrasound-guided fine needle aspiration or on an intraoperative frozen section, therapeutic LND (level II-V) was conducted. After primary surgery, partial patients were administered a therapeutic dose of RAI dependent on outcomes of surgery in the next 1–2 months.

Off-Tg and on-Tg levels were evaluated in the patients received RAI therapy. Neck ultrasound, serum-free thyroxine, thyroid stimulating hormone (TSH), maximum unstimulated Tg (uTg, didn’t include on-Tg) and

TgAb were tested every 3 months the first year, every 6 months for the second year, and thereafter annually[13].

Definitions

Off-Tg is defined as the Tg levels in condition of increased TSH to > 70 IU/ml before RAI therapy and on-Tg is defined as the Tg levels in condition of thyroid hormone replacement after RAI therapy[1]. The maximum uTg < 0.2 ng/mL, on-Tg < 0.2 ng/mL and off-Tg < 1 ng/ml were deemed as negative Tg levels in the absence of interfering TgAb[1]. TgAb > 115 U/mL were considered positive TgAb levels in our center which could result in interference for Tg levels. All recurrent LNs were verified as structural recurrence with neck ultrasound. A fine needle aspiration was conducted to confirm the recurrence and then a therapeutic neck dissection was performed in recurrent levels.

Grouping And Variables

Patients were divided into two groups with different Tg levels in different comparisons. Groups were first set up by maximum uTg levels using a cut-off level of 0.2 ng/mL. As for patients who were administered RAI therapy, they were divided into two groups by off-Tg with 1 ng/mL cut-off or by on-Tg with 0.2 ng/mL cut-off.

The following data were thoroughly reviewed as potential risk factors for positive Tg levels. (1) Demographic data and basic information: Age, sex, body mass index (BMI), nodular goiter (NG), hashimoto's thyroiditis (HD), hypertension, diabetes, hyperthyroidism. (2) Information of operation: surgical strategy and extent. (3) Surgical outcomes: harvested LNs, metastatic LNs, metastatic rate of LNs, diameters of recurrent LNs. (4) Oncological data: tumor size, multifocality, bilaterality, TNM stage, extranodal extension.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation. The $\chi 2$ test or Fisher exact test was used to evaluate the differences of incidences, and the student's t-test and/or analysis of variance was used to evaluate the differences of continuous variables. Based on the variables that were statistically significant or P value < 0.10 in univariate analysis, multivariate analysis with logistic regression was conducted to identify the independent risk factors. The variable was re-coded from a continuous variable into a dichotomous variable according to the optimal cut-off value produced by the receiver operator characteristic (ROC) curve analysis for multivariate analysis. The results of the multivariate analysis were reported in odds ratio (OR) and 95% confidence interval (CI). Two-sided P < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 25.0 for Windows (IBM Corp., Armonk, NY).

Results

Patient characteristics

This study included 60 patients (18 males and 42 females) and the details of flow chart were shown in Fig. 1. Mean age was 44.1 ± 13.8 years (interquartile range, IQR, 33−54 years). Age ≥ 45 and ≥ 55 were 29 (48.3%) and 14 (23.3%) patients, respectively. Forty-nine (81.7%) patients underwent RAI therapy. The characteristics of the patients are presented in Table 1. The mean size of the tumor was 21.7 ± 14.3 mm and tumors > 40 mm were found in 7 (11.7%) patients. Multifocality and bilaterality were identified in 11 (18.3%) and 8 (13.3%) patients, respectively. T3 tumors were found in 16 (26.7%) patients. T4 tumors were found in 19 (31.7%) patients. The mean numbers of total harvested and involved LNs were 33.0 ± 20.8 and 8.5 ± 8.2, respectively.

Table 1
Characteristics of the Patients (N = 60)

Variable	**N**	**%**
Ages, yrs, mean ± SD (IQR)	44.1 ± 13.8 (33–54)	-
≥ 45	29	48.3
≥ 55	14	23.3
Sex, male/female	18/42	30.0/70.0
BMI	23.1 ± 3.7	
NG	24	40.0
HD	8	13.3
Hypertension	5	8.3
Diabetes	3	5.0
Hyperthyroidism	5	8.3
Hypothyroidism	0	0
Tumor size (primary), mm,		
Mean ± SD (IQR)	21.7 ± 14.3 (10.75–22.25)	
> 40 mm	7	11.7
Multifocality (primary)	11	18.3
Bilaterality (primary)	8	13.3
TgAb positive (> 115U/mL)	8	13.3
TNM stage (primary)		
Tx/T1/T2/T3/T4	8/11/6/16/19	13.3/18.3/10.0/26.7/31.7
Nx/N0/N1a/N1b	0/11/12/37	0/18.3/20.0/61.7
Mx/M0/M1	1/59/0	1.7/98.3/0
Surgical strategy		
iCND/bCND	4/15	6.7/25.0
iCND + iLND	7	11.7

BMI: Body Mass Index; HD: Hashimoto's disease; NG: nodular goiter; iCND: ipsilateral central neck dissection; bCND: bilateral central neck dissection; iLND: ipsilateral lateral neck dissection; bLND: bilateral lateral neck dissection; LN: lymph node.

Variable	N	%
bCND + iLND	24	40.0
bCND + bLND	10	16.7
Harvested LNs	33.0 ± 20.8	
Metastatic LNs	8.5 ± 8.2	
Ratio of Metastatic LNs %	29.5 ± 23.1	
RAI Administration	49	81.7
Central LNs recurrence	19	31.7
Lateral LNs recurrence	36	60.0
Central & lateral LNs recurrence	5	8.3
Diameters of recurrent LNs, mm, Mean ± SD (IQR)	18.7 ± 12.9 (10.75-22.00)	
Extranodal extension	20	33.3
BMI: Body Mass Index; HD: Hashimoto's disease; NG: nodular goiter; iCND: ipsilateral central neck dissection; bCND: bilateral central neck dissection; iLND: ipsilateral lateral neck dissection; bLND: bilateral lateral neck dissection; LN: lymph node.		

Follow-up

During the median follow-up of 29 months (range, 13-78months), 8 (13.3%) patients maintained TgAb-positive (TgAb > 115U/mL). Central, lateral and both compartments LN recurrence were noted in 19 (31.7%), 36 (60.0%) and 5 (8.3%) patients, respectively. The mean diameter of the largest recurrent LN was 18.7 ± 12.9 mm. Extranodal extensions were observed in 20 (33.3%) patients. At the latest follow-up, all patients were alive and disease-free.

Maximum uTg levels ≥ 0.2 ng/mL were detected in 42 (70%) patients and maximum uTg levels < 0.2 ng/mL were found in 18 (30%) patients during follow-up. In 49 patients who underwent RAI treatment, 34 (69.4%) were with an off-Tg ≥ 1 ng/mL and 15 (30.6%) were with an off-Tg < 1 ng/mL, while 31 (63.3%) were with an on-Tg ≥ 0.2 ng/mL and 18 (36.7%) were with an on-Tg < 0.2 ng/mL.

Meanwhile, in 52 patients with TgAb-negative (< 115U/mL), 39 (75.0%) and 13 (25.0%) patients were appeared with maximum uTg levels ≥ 0.2 ng/mL and < 0.2 ng/mL respectively (Table 2). Forty-three patients received RAI and 33 (76.7%) of them were with an off-Tg ≥ 1 ng/mL, and 10 (23.3%) of them were with an off-Tg < 1 ng/mL (Table 3), while 30 (69.8%) were with an on-Tg ≥ 0.2 ng/mL and 13 (30.2%) were with an on-Tg < 0.2 ng/mL (Table 4).

Table 2
Comparisons of maximum uTg with TgAb negative

	uTg ≥ 0.2 ng/ml (N = 39)	uTg < 0.2 ng/ml (N = 13)	P
Age, yrs	47.2 ± 14.1	39.2 ± 12.1	0.074
Sex (male)	15	3	0.502
BMI	23.7 ± 3.9	22.5 ± 3.8	0.353
NG	16	6	0.746
HD	5	1	1.000
Hypertension	4	2	0.632
Diabetes	2	1	1.000
Hyperthyroidism	3	2	0.589
Tumor size (primary), mm	21.7 ± 13.3	18.9 ± 10.4	0.498
Multifocality (primary)	4	5	0.033*
Bilatrality (primary)	4	2	0.632
Surgical strategy			
iCND	2	1	1.000
bCND	11	4	1.000
bCND + iLND	20	8	0.403
bCND + bLND	8	1	0.403
Harvested LNs	32.7 ± 21.6	40.5 ± 19.7	0.256
Metastatic LNs	9.6 ± 8.8	5.9 ± 7.3	0.181
Ratio of Metastatic LNs %	34.1 ± 25.7	14.4 ± 10.5	0.001*
Diameter of recurrent LNs	21.1 ± 14.7	14.6 ± 5.6	0.027*
≥ 25 mm	13	0	0.023*
Extranodal extension	15	5	1.000

BMI: Body Mass Index; HD: Hashimoto's disease; NG: nodular goiter; iCND: ipsilateral central neck dissection; bCND: bilateral central neck dissection; iLND: ipsilateral lateral neck dissection; bLND: bilateral lateral neck dissection; LNs: lymph nodes.

* means significantly statistical differences

Table 3
Comparisons of Off-Tg with TgAb negative and RAI administration

	Off-Tg ≥ 1 ng/ml (N = 33)	Off-Tg < 1 ng/ml (N = 10)	P
Age, yrs	46.2 ± 14.3	38.4 ± 16.0	0.147
Sex (male)	13	3	0.719
BMI	23.4 ± 3.5	22.5 ± 3.3	0.442
NG	16	3	0.470
HD	4	1	1.000
Hypertension	3	1	1.000
Diabetes	1	1	0.415
Hyperthyroidism	3	2	0.589
Tumor size (primary), mm	22.7 ± 14.0	18.7 ± 11.0	0.412
Multifocality (primary)	3	4	0.040*
Bilatrality (primary)	3	1	1.000
Surgical strategy			
iCND	0	0	-
bCND	7	2	-
bCND + iLND	19	7	0.645
bCND + bLND	7	1	0.645
Harvested LNs	37.6 ± 20.8	38.2 ± 21.8	0.941
Metastatic LNs	10.3 ± 9.2	6.8 ± 8.2	0.287
Ratio of Metastatic LNs %	29.8 ± 23.6	16.3 ± 10.7	0.089
Diameter of recurrent LNs	23.0 ± 15.0	15.6 ± 4.7	0.018*
≥ 25 mm	13	0	0.020*
Extranodal extension	11	6	0.158

BMI: Body Mass Index; HD: Hashimoto's disease; NG: nodular goiter; iCND: ipsilateral central neck dissection; bCND: bilateral central neck dissection; iLND: ipsilateral lateral neck dissection; bLND: bilateral lateral neck dissection; LNs: lymph nodes.

* means significantly statistical differences

Table 4
Comparisons of on-Tg with TgAb negative and RAI administration

	On-Tg ≥ 0.2 ng/ml(N = 30)	On-Tg < 0.2 ng/ml (N = 13)	P
Age, yrs	47.2 ± 14.5	38.0 ± 14.2	0.062
Sex (male)	12	4	0.735
BMI	23.4 ± 3.5	22.9 ± 3.3	0.679
NG	13	6	0.864
HD	4	1	1.000
Hypertension	3	1	1.000
Diabetes	1	1	0.518
Hyperthyroidism	2	0	1.000
Tumor size (primary), mm	22.6 ± 14.0	19.9.0 ± 11.8	0.556
Multifocality (primary)	2	5	0.019*
Bilatrality (primary)	2	2	0.572
Surgical strategy			
iCND	0	0	-
bCND	6	3	-
bCND + iLND	17	9	0.385
bCND + bLND	7	1	0.385
Harvested LNs	38.4 ± 20.5	36.3 ± 22.3	0.766
Metastatic LNs	10.9 ± 9.4	6.2 ± 7.4	0.120
Ratio of Metastatic LNs %	29.9 ± 24.0	19.1 ± 14.4	0.141
Diameter of recurrent LNs	23.6 ± 15.5	16.0 ± 4.7	0.020*
≥ 25 mm	13	0	0.004*
Extranodal extension	11	6	0.559

BMI: Body Mass Index; HD: Hashimoto's disease; NG: nodular goiter; iCND: ipsilateral central neck dissection; bCND: bilateral central neck dissection; iLND: ipsilateral lateral neck dissection; bLND: bilateral lateral neck dissection; LNs: lymph nodes.

* means significantly statistical differences

Univariate Analyses Of Factors Associated With Positive Tg Levels

The maximum uTg ≥ 0.2 ng/mL were significantly associated with older age, higher possibility of diameters of recurrent LNs ≥ 25 mm and higher LNs metastatic rate (P = 0.024, 0.045 and 0.039, respectively). In 49 patients underwent RAI treatment, off-Tg ≥ 1 ng/mL were significantly associated with older age, larger diameter of recurrent LNs and higher possibility of diameters of recurrent LNs ≥ 25 mm (P = 0.042, 0.021 and 0.038, respectively). Older age, larger diameter of recurrent LNs and higher possibility of diameters of recurrent LNs ≥ 25 mm were also seen in patients with on-Tg ≥ 0.2 ng/ml (P = 0.017, 0.020 and 0.008, respectively). However, lower rate of multifocality of the primary tumor was found in patients with off-Tg ≥ 1 ng/mL and on-Tg ≥ 0.2 ng/ml (P = 0.047 and 0.039, respectively).

When excluding the interference of TgAb-positive (Table 2), the maximum uTg levels ≥ 0.2 ng/ml were significantly associated with larger diameter of recurrent LNs (P = 0.027), higher possibility of diameters of recurrent LNs ≥ 25 mm (P = 0.023), lower rate of multifocality (P = 0.033) and higher LN metastatic rate (P < 0.001). In the 43 patients with TgAb-negative who underwent RAI treatment, off-Tg ≥ 1 ng/mL (Table 3)was significantly associated with larger diameter of recurrent LNs (P = 0.018), higher possibility of diameters of recurrent LNs ≥ 25 mm (P = 0.020) and lower multifocality rate (P = 0.040). Larger diameter of recurrent LNs (P = 0.020), higher possibility of diameters of recurrent LNs ≥ 25 mm (P = 0.004), and lower rate of multifocality (P = 0.019) were also seen in patients (Table 4) with on-Tg ≥ 0.2 ng/mL (P = 0.020 and 0.019, respectively).

Independent Predictors Of Positive Tg Levels

In multivariate analysis, the number of metastatic LNs ≥ 8 was an independent predictor for maximum uTg ≥ 0.2 ng/mL in patients with TgAb-negative (OR = 8.767; 95% CI = 1.392−55.216; P = 0.021), while multifocality was an independent protective factor for maximum uTg ≥ 0.2 ng/mL (OR = 0.123; 95% CI = 0.020−0.762; P = 0.024) as shown in Table 5. As for patients received RAI with TgAb-negative, the ratio of metastatic LNs ≥ 25% was an independent predictor for off-Tg ≥ 1 ng/mL (OR = 20.997; 95% CI = 1.649-267.384; P = 0.019). However, no significant differences were found in the multivariate analysis for predictors of on-Tg ≥ 0.2 ng/mL.

Table 5
Multivariate analysis of predictors of maximum uTg ≥ 0.2 ng/mL with TgAb negative

	P	OR	95% CI
Multifocality	0.024*	0.123	0.020–0.762
Number of metastatic LNs ≥ 8	0.021*	8.767	1.392–55.216
OR: odds ratio; CI: confidence interval; LNs: lymph nodes.			
* means significantly statistical differences			

Discussion

We included all PTC patients with LN recurrence and tried to find out differences between groups of Tg-negative and Tg-positive during the follow-up. Our current study cohort was well followed for a relatively long period of median 29 months but with a small sample size (60 patients). Though many PTC patients underwent secondary surgery for recurrence in our center, the primary treatment of partial them were performed elsewhere and it became difficult to obtain the whole and correct data. In order to ensure the integrality and avoid bias of incomplete outcomes, we decided to make strict inclusive criteria other than simply enlarging the sample size. It was recognized that positive TgAb levels would affect the serum Tg levels and some studies excluded all patients with TgAb-positive to avoid potential interference[8,14]. The recent study concluded that TgAb interference limits Tg utility as a tumor marker in 30% of TgAb-positive patients[15]. However, we didn't exclude patients with TgAb-positive in our study for we found the serum Tg levels of all patients with TgAb-positive were far away from the cut-off value and won't result in bias when grouping dependent on cut-off values. Nevertheless, to ensure the most preciseness, subgroup excluding patients with TgAb-positive was conducted.

Our outcomes indicated that patients with maximum uTg ≥ 0.2 ng/mL were significantly associated with older age, diameters of recurrent LNs ≥ 25 mm and higher LNs metastatic rate during primary surgery. Ages are often associated with tumor malignancy and 55 years old was regarded as a cut-off age in the 8th edition AJCC staging system[12]. However, age was no longer an independent predictor when we excluded patients with TgAb-positive. Higher metastatic rates seen in the maximum uTg ≥ 0.2 ng/mL group further indicated tumor malignancy and invasiveness.

In patients underwent RAI treatment after primary surgery, ages were found at the same condition as mentioned above. Positive off-Tg levels and positive on-Tg levels were significantly associated with larger diameter of recurrent LNs. The sources of Tg were recurrent LNs and theoretically the levels of Tg depended on numbers of recurrent LNs and size of each recurrent LNs when there were no other remnant areas, and the levels of Tg were also regulated by TSH levels. No difference of numbers of metastatic LNs and TSH levels was found when conducting analysis of positive and negative groups of off-Tg or on-Tg. This similar trend was observed in comparisons between maximum uTg-positive group and maximum uTg-negative group for all included patients though we expected significant differences. This might be resulting from the large proportion of RAI patients (81.7%) which led to this trend and possibly existed remnant thyroid or tumor tissues in patients without RAI administration shared the source which led to the no difference. RAI administration was considered the effective way to ablate remnant thyroid tissue though incomplete structural response might happen sometimes[16].

Off-Tg testing is recommended to obtain the best follow-up accuracy for the detection of recurrent or persistent disease than on-Tg[17]. In the multivariate analysis, the ratio of metastatic LNs ≥ 25% was the only independent predicator for off-Tg ≥ 1 ng/mL, while no predicator was found with significant differences in on-Tg ≥ 0.2 ng/mL. A recent study showed an initial off-Tg level of 5.0 ng/mL was involved in the highest sensitivity and specificity for predicting recurrence[8]. It is consistent with the findings of the previous study that defined the cut-off of positive or negative value at 4.2 ng/mL[18]. However, off-Tg < 1 ng/mL was considered negative in our analysis for a recent study suggested that off-Tg levels were correlated with structural incomplete response: 0% structural incomplete response with the off-Tg levels of < 1 ng/mL, 1.73% with the off-Tg levels of 1–10 ng/mL, and 42.74% with the off-Tg levels of > 10 ng/mL, which corresponded to the guideline (2015)[1,7]. Orlov et al. proposed that patients with an off-Tg < 1 ng/mL should not receive RAI and those with off-Tg 1–5 ng/mL should be further evaluated based on repeat off-Tg levels and pathologic features[19]. However, the proportion (10/43, 23.3%) of patients with off-Tg negative (< 1 ng/mL) was not low as expected in patients with LNs recurrent. Thus, we thought the cut-off value of off-Tg in patients with risk of structural recurrence should be discussed further. Meanwhile, number of metastatic LNs ≥ 8 showed an independent indicator for maximum uTg ≥ 0.2 ng/mL. Alexandria et al. similarly proposed a strategy to use maximum uTg levels for clinical decision making rather than off-Tg levels.[16] Patients with maximum uTg ≥ 0.2 ng/mL do benefit from RAI administration as it effectively ablates remnant thyroid tissue, which may allow for easier biomedical detection of recurrence.[16] Our results suggest patients with maximum uTg < 0.2 ng/mL already achieved an excellent response from surgery with similar number of harvested LNs and lower ratio of metastatic LNs but still require attention on imaging during follow-up.

Our analysis did have limitations inherent in its study design. The data were retrospectively collected and of a relatively small sample size. In addition, a lot of patients were excluded for incomplete data of Tg and primary surgery. We only focused on LNs recurrence, and other types of recurrence such as distant recurrence and biochemical recurrence were not analyzed. The accurate time of the recurrent was difficult to decide.

Conclusions

This study found Tg-positive was associated with larger size of recurrent LNs. Number of metastatic LNs ≥ 8 could independently predict maximum uTg-positive with TgAb-negative. The ratio of metastatic LNs ≥ 25% was an independent predicator for off-Tg-positive with TgAb-negative and RAI administration. RAI administration seems to benefit the value of Tg measurement during follow-up. However, importantly, imaging examinations need to be further applied for Tg-negative patients on account of difficulty on detecting Tg with smaller LNs, especially for patients without RAI ablation.

Abbreviations

Tg: serum thyroglobulin; PTC: papillary thyroid carcinoma; LNs: lymph nodes; TT: total thyroidectomy; RAI: radioactive iodine; uTg: unstimulated Tg; off-Tg: pre-RAI ablation serum-stimulated Tg; on-Tg: unstimulated Tg detected at 1 week after RAI ablation; CND: central neck dissection; LND: lateral neck dissection; TgAb: anti-thyroglobulin antibody; TSH: thyroid stimulating hormone; BMI: body mass index; NG: nodular goiter; HD: hashimoto's thyroiditis; ROC: receiver operator characteristic; OR: odds ratio; CI: confidence interval.

Declarations

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Author's contributions

ZX and YQ designed this study. ZX, YQ, ZL, LZ, and YF were responsible for data collection. ZL, LZ, YF were responsible for analysis and interpretation of the data. ZX and YQ participated in the analysis of data and drafted the manuscript. JZ and AS contributed to the conception and design of the study and revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Datasets from the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was in accordance with the Declaration of Helsinki and has been approved by the ethics committee of West China Hospital, Sichuan University.

Consent for publication

Not applicable

Competing interests

All authors report no conflicts of interest in this work.

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Figures

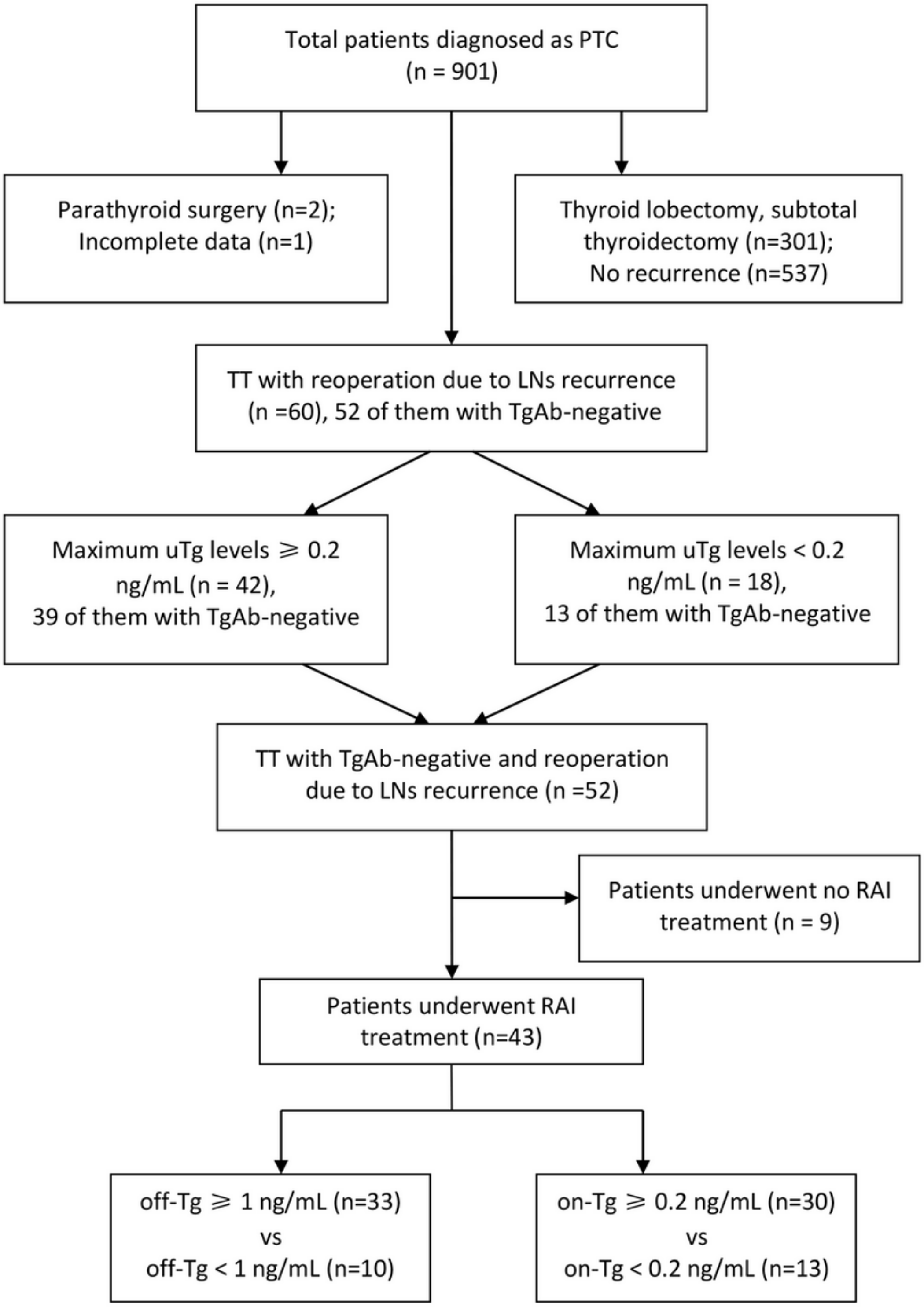

Figure 1

Flow chart of patients reviewed PTC, papillary thyroid carcinoma; TT, total thyroidectomy; LNs, lymph nodes; Tg, thyroglobulin; TgAb, anti-thyroglobulin antibody; uTg, maximum unstimulated Tg; RAI, radioactive iodine; off-Tg, Pre-RAI ablation serum-stimulated Tg; on-Tg, unstimulated Tg detected at 1 week after RAI ablation.