Prediction of Ipsilateral Lateral Cervical Lymph Node Metastasis in Papillary Thyroid Carcinoma: A Combined Dual-energy CT and Thyroid Functional Indicators Study

Ying Zou
First teaching hospital of Tianjin University of Traditional Chinese Medicine
Huanlei Zhang
Tianjin First Central Hospital
Wenfei Li
Tianjin First Central Hospital
Yu Guo
Tianjin First Central Hospital
Fang Sun
Tianjin First Central Hospital
Yan Shi
Binzhou Medical University Hospital
Yan Gong
Tianjin First Central Hospital
Xiudi Lu
First Teaching Hospital of Tianjin University of Traditional Chinese Medicine
Wei Wang
tianjin first central hospital
Shuang Xia (xiashuang77@163.com)
Tianjin First Center Hospital https://orcid.org/0000-0003-1626-6383

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Abstract

Background

The prediction of ipsilateral lateral cervical lymph node metastasis (ipsi-LLNM) was crucial to the operation plan in patients with papillary thyroid carcinoma (PTC). This study aimed to investigate the risk factors for ipsi-LLNM using dual-energy computed tomography (DECT) and thyroid functional indicators in patients with PTC.

Methods

The medical records of 406 patients with a pathological diagnosis of PTC were retrospectively reviewed from Jan 2016 to Dec 2019. Demographic, clinical, pathological findings, and parameters from DECT were evaluated. Risk factors for ipsi-LLNM were explored by univariate and multivariate analyses. Receiver operating characteristic (ROC) curves were used to evaluate the cut-off value of each risk factor.

Results

Totally 406 patients with PTC were analyzed, including 128 with ipsi-LLNM and 278 without. There were statistical differences of parameters between the two groups ($P < .0001$), including serum Tg, Anti-Tg, Anti-TPO, the volume of the primary lesion, calcification, extrathyroidal extension (ETE), and iodine concentration (IC) in arterial and venous phases. Independent risk factors for ipsi-LLNM included serum Tg, Anti-Tg, ETE, and IC in arterial and venous phases ($P < .05$). Ipsi-LLNM was more likely to occur when the following conditions were met: with ETE, Tg > 100.01 ng/ml, Anti-Tg > 89.43 IU/ml, IC in arterial phase > 3.4 mg/ml and IC in venous phase > 3.1 mg/ml.

Conclusions

Application of DECT parameters and thyroid functional indicators can improve the diagnostic performance in the evaluation of ipsi-LLNM in patients with PTC.

Background

The incidence of papillary thyroid carcinoma (PTC) has dramatically increased during recent years (1), and it's well established that PTC has a strong propensity for lymph node metastasis (LNM) (2), which may increase the recurrence and shorten survival (3, 4). According to the American Thyroid Association (ATA) management guidelines for adult patients with thyroid cancer (5), lateral cervical lymph nodes dissection (LLND) should be performed in patients with N1 stage, which is defined as the presence of regional LNM. However, prophylactic LLND for low-risk patients (e.g., no clinical or radiographic evidence of invasion or metastases) (5) will undoubtedly increase the probability of postoperative complications. Therefore, it is important to identify the presence of lateral cervical LNM (LLNM) and their range before operation as accurately as possible.

Preoperative imaging examination plays an important role in the detection and staging of LLNM in patients with PTC (6). However, ultrasound (US), which is the first-choice examination method for thyroid cancer (7), has high specificity but low sensitivity for lateral cervical lymph node examination (8-10). Therefore, for most lymph nodes without typical characteristics, US examination is still insufficient. Moreover, US is greatly affected by the operators' experience and manipulation (11), and cannot achieve quantitative measurement. Dual-energy computed tomography (DECT) is widely used to help differentiate metastatic from benign lymph nodes in patients with PTC in recent years (12-17). The reasons for the application of DECT in PTC patients are stated in Supplement 1. And we have good reasons to prove that the possible potential delay in postoperative radioactive iodine (RAI) therapy caused by the use of iodinated contrast agents will not cause harm for PTC patients. The detailed reason was in Supplement 2. Previous studies have shown that the combination of venous phase λ_{HU} and arterial phase normalized iodine concentration (NIC) showed higher accuracy for the preoperative diagnosis of LNM (17). But the measurement object was a lymph node, which is complicated and hard to achieve a one-to-one correspondence between DECT and pathology in clinical work. In addition, DECT-based radiomic nomogram improved the preoperative prediction of cervical LNM in patients with PTC, and the area under the receiver operating characteristic (ROC) curve (AUC) was 0.807 to 0.910 in the training cohort (14, 18). However, the above studies have focused on LNM, not just LLNM. Therefore, it is not sure whether DECT can accurately predict LLNM before operation.

Some studies (19, 20) have shown that thyroid stimulating hormone (TSH) is closely related to the occurrence and development of PTC, but the relationship between other thyroid functional indicators and LLNM is inconclusive, for example, preoperative serum thyroglobulin (Tg), anti-thyroid stimulating hormone (Anti-Tg) and anti-thyroid peroxidase (Anti-TPO).

In the current study, we hypothesized that parameters of the primary lesion from DECT and thyroid functional indicators were potentially associated with LLNM in patients with PTC. The purpose of the study was first, to evaluate the possible correlation of iodine concentration (IC) in arterial and venous phases of the primary lesion among PTC patients and ipsi-LLNM before treatment. Second, to analyze whether preoperative laboratory examination indicators, such as serum Tg, Anti-Tg, Anti-TPO were related to ipsi-LLNM.

Methods

Patients population

This retrospective study was approved by the ethics committee of Tianjin First Central Hospital (2019N153KY), and the requirement for written informed consent was waived since the retrospective nature. From January 2016 to December 2019, a total of 644 consecutive patients who were diagnosed with thyroid malignancy by US-guided fine-needle aspiration (US-FNA) were initially selected. To ensure the accuracy of measurement and the independence of included parameters, we only included patients with a single lesion. They all underwent total thyroidectomy or thyroid lobectomy with central and

ipsilateral LLND, due to suspected LLNM according to the preoperative US and/or DECT examination. We conducted US follow-up for at least half a year after surgery and proved that the included patients did not have LNM in the contralateral cervical region. At length, among them, medical records and DECT images of 406 consecutive patients (84 male, mean age, 45.86 years ± 13.98; 322 female, mean age, 47.14 years ± 12.56) were reviewed. Inclusion and exclusion criteria were detailed in the flowchart (Figure 1). Refer to Supplement 3 for specific US and CT diagnostic criteria of cervical LNM in patients with PTC.

Image acquisition and processing

All data were scanned by using a 64 multi-detector row CT scanner (Somatom Defination Flash, Siemens Healthcare, Forchheim, Germany) with dual-phase contrast-enhanced CT. The detailed CT protocol was provided in Supplement 4.

Study design

Baseline information, including age, sex, final pathology diagnosis, preoperative serum Tg, Anti-Tg, and Anti-TPO among PTC patients was obtained from the medical record. The reference range of each index was listed in Table S1. Histopathological variables were extracted from pathology reports including tumor location (left lobe, right lobe, or isthmus), regional LNM, concomitant Hashimoto's thyroiditis (HT), or nodular goiter. In this study, to describe the lesion more accurately, we used volume instead of diameter. Two radiologists who were experienced at head and neck disease with over 10 years of experience used ImageJ software (public software, version ImageJ v1.8.0) to measure the volume separately. And the two radiologists independently performed a DECT review to confirm image characteristics of primary focus, including cystic degeneration, calcification, extrathyroidal extension (ETE), IC in arterial and venous phases. Manual freehand delineation of a region of interest (ROI) was performed on three different adjacent slices containing the largest lesion area to measure IC of each lesion. ROI was placed in the solid part with an area at least greater than 2 mm^2 including the whole lesion (Figure S1). The average value from three measurements was taken for the final evaluation. Two radiologists were blinded to clinical data and pathological diagnosis. A week later, all lesions were retested. Intra and inter-observer consistency analyses were performed. Tumor pathology was classified according to the 2017 World Health Organization (WHO) published recommendations and the American Joint Committee on Cancer (AJCC) 8th edition (21).

Explanation of related concepts

Fuzzy boundaries and/or invasion into adjacent tissues were considered to indicate ETE on DECT images. Central cervical lymph nodes (levels VI) and lateral cervical lymph nodes (levels II-V) removed by the surgeon were assessed as evidence of regional LNM.

Patients included in this study were all performed total thyroidectomy or lobectomy with central and ipsilateral LLND on the premise that preoperative US or DECT proved the presence of metastatic lymph nodes. Different surgical procedures were chosen for thyroid lesions and lymph nodes. The extent of

lymph node dissection was according to the Chinese Society of Clinical Oncology (CSCO) guidelines (22) and ATA guidelines (5). Bilateral central cervical lymph nodes dissection (CLND) included the removal of pre-laryngeal, pretracheal, and both the right and left paratracheal nodal basins. Ipsilateral CLND included pre-laryngeal, pretracheal, and paratracheal nodal basins on the side of the tumor. LLND was defined as compartment oriented functional lateral neck dissection, including levels II to V.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 21.0 (IBM, Armonk, NY), and GraphPad prism 8.3.0 and Medcalc 18.2.1 were used to draw graphs. A consistency test was performed to test the agreement of quantitative parameters of DECT between the two radiologists. The chi-square analysis was calculated for categorical variables, including age, sex, location, HT, nodular goiter, cystic degeneration, calcification, and ETE. We divided the patients into two groups based on age using 55-year-old as a cut-off value according to the 8th AJCC staging systems (23). The t-test was used for continuous variables including Tg, Anti-Tg and Anti-TPO, volume, IC in the arterial phase, and IC in the venous phase. Univariate analysis was performed using Student's T-tests for normally distributed data and Mann-Whitney U test for continuous variables that were not normally distributed. We specified a priori that variables with an overall *P* value less than 0.05 on univariate analysis would be candidate variables for the multivariable binary logistic regression model. Subsequently, candidate variables were entered as independent variables into a binary logistic backward stepwise regression analysis to select the independent predictors (24). At each step, the variable with the highest *P* value was eliminated until the remaining variables had *P* values < 0.05 and were included in the prediction model. Statistical significance for analysis was determined to be *P* value < 0.05.

Results

Baseline Characteristics

Among 406 patients, LLNM was detected in 128 patients, which accounted for 31.5%. Of note, there were 16 patients (16 of 128) with skip metastases, meaning LLNM without central cervical lymph node metastasis (CLNM) (Table S2). Baseline information and DECT images characteristics of primary foci according to LLNM status were summarized in Table 1. The median age was 48 years (IQR 36 - 57 years, range 22 - 77 years). The majority of patients were female (322 patients, 79.3%; 50 years, IQR 39 - 58 years), and 20.7% (84 patients) were male (41 years, IQR 32 - 55 years). 149 primary foci (36.7%) were with cystic degeneration, 85 primary foci (21.0%) were with calcification, and 104 primary foci (25.6%) were with ETE. The above parameters were statistical significance for differentiation between patients with LLNM and without (*P* < .05). Check the specific information about other parameters in Table 1.

Result of consistency analysis

The intraclass correlation coefficient (ICC) calculated for the agreement of features extracted by two radiologists ranged from 0.913 to 0.974, reflecting good agreement (*P* .000). The imaging characteristics

of DECT were basically consistent between the two radiologists. The inter-observer and intra-observer consistency analysis for all the parameters was greater than 0.8, which showed good consistency (Table S3, Figure S2).

Comparison of DECT imaging parameters and thyroid functional indicators between patients with and without ipsi-LLNM

Quantitative parameters of patients with and without LLNM were listed in Table 2. Tg, Anti-Tg, Anti-TPO, volume, IC in the arterial phase, and IC in the venous phase were higher in those with LLNM than those without ($P < .0001$) (Table 2, Figure 2).

Univariate and multivariate logistic regression analysis of risk factors for ipsi-LLNM in patients with PTC

Univariable logistic regression analysis showed that Tg, Anti-Tg, volume, cystic degeneration, calcification, ETE, IC in the arterial phase, and IC in the venous phase were risk factors for predicting the presence of LLNM (*P* range, .000 - .006). Further multivariable logistic regression analysis showed that among these parameters, Tg (OR, 2.668; 95% CI: 1.590, 4.475; *P* .000), Anti-Tg (OR, 2.001; 95% CI: 1.202, 3.333; *P* .008), ETE (OR, 6.335; 95% CI: 3.768, 10.651; *P* .000), IC in arterial phase (OR, 3.691; 95% CI: 2.170, 6.278; *P* .000) and IC in venous phase (OR, 2.122; 95% CI: 1.271, 3.541; *P* .004) were the independent predictors for LLNM. Sex, age, Anti-TPO, HT, nodular goiter, volume, cystic degeneration, and calcification were not related to LLNM in patients with PTC ($P > .05$) (Table 3).

The cut-off value of each parameter for ipsi-LLNM in patients with PTC

The AUC, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for differentiating ipsi-LLNM for each parameter were listed in Table 4. ROC curve analysis determined that the optimal cut-off points for Tg, Anti-Tg, IC in arterial phase and IC in venous phase in predicting ipsi-LLNM were 100.01 ng/ml (AUC 0.856, 95%CI 0.818-0.889), 89.43 IU/ml (AUC 0.766, 95%CI 0.721-0.806), 3.4 mg/ml (AUC 0.846, 95%CI 0.807-0.879) and 3.1 mg/ml (AUC 0.777, 95%CI 0.733-0.816), respectively. The specific information of other parameters was listed in Table 4, Figure 3 and S3. There were two examples of predicting ipsi-LLNM, which might help illustrate the predictive value of these independent risk factors (Figure 4 and 5).

Discussion

In this retrospective study, we evaluated the predictors and cut-off value of each parameter for LLNM in 406 patients with PTC. There were three important findings in the current study. First, IC in arterial phase > 3.4mg/ml and IC in the venous phase > 3.1mg/ml of primary lesions were positively associated with the risk of ipsi-LLNM in patients with PTC. Second, Tg > 100.01ng/ml and Anti-Tg > 89.43 IU/ml were another two independent risk factors for ipsi-LLNM. Third, the combined application of DECT quantitative parameters and thyroid functional indicators can improve the diagnostic performance in the evaluation of ipsi-LLNM in patients with PTC to some extent.

In the present study, IC in arterial and venous phases of the primary lesion were both independent risk factors for LLNM in patients with PTC. In Liu's study (17), DECT was used to quantitatively assess cervical LNM in PTC. Compared with their study, we had a much larger sample size (406 vs. 52), and the AUC of IC in the arterial phase in our study (0.846) was slightly higher than theirs (0.811). And we chose the primary focus as the prediction target, reducing the possible errors caused by pathology and lymph node one-to-one correspondence. As well known, IC was a highly sensitive and specific parameter for identifying benign and malignant thyroid nodes (25, 26), which was a direct response to blood flow and affected by the number of blood vessels (27). Normal follicular cells, responsible for thyroid iodine uptake, exist in benign conditions such, whereas in PTC, they were replaced by cancer cells or fibrous tissues. The specific iodine absorption characteristics of thyroid tissue and the changed in tumor-related vascular patterns in lymph nodes were also correlated with IC. Therefore, the differences in the iodine uptake might lead to lymph nodes metastatic capacity. We speculated that the higher the IC of the primary foci, the greater the probability of occurrence of LLNM.

Tg was an important tumor marker for PTC patients (28). And there was mutual influence between Tg and Anti-Tg (29). Anti-Tg and Anti-TPO were closely related to the occurrence of PTC (30). Most previous studies had demonstrated that PTC may indeed lead to an autoimmune reaction characterized by circulating thyroid functional indicators (31). However, whether these indicators could be potential predictive factors of ipsi-LLNM has not been proved before. In the current study, univariate analysis results suggested that Tg and Anti-Tg were related to ipsi-LLNM (*P* range, .000 - .001). Further multivariate analysis showed that Tg > 100.01ng/ml and Anti-Tg > 89.43 IU/ml were also independent risk factors for ipsi-LLNM, which was in agreement with Li's reports (19). Based on these results, we may conclude that Tg and Anti-Tg may be correlated with tumor aggressiveness and prognosis in patients with PTC, and the measurement could give additional information for predicting aggressiveness and ipsi-LLNM. Therefore, we suggest that surgeons should pay more attention to the levels of Tg and Anti-Tg, which may have potential predictive value for ipsi-LLNM.

Besides, ETE was also an independent predictor for ipsi-LLNM, which was consistent with previous studies (32-37). We considered that the more aggressive the tumor, the greater the probability of LNM.

It is worth noting that in the current study, of 128 patients with LLNM, 16 patients developed skip metastasis (12.5%), which was consistent with previous research (38-41). Unfortunately, due to the small number of cases, in this study, we cannot count the risk factors related to skip metastasis. In the future, after expanding the sample size, we will do further research.

The present study has some limitations due to its retrospective design. First, because of its retrospective nature and single-center analysis, patient volume and inspection items could not be designed beforehand. A potential selection bias may exist. Because of this, we cannot get accurate postoperative pathological information about the size of metastatic lymph nodes, so we cannot predict micro-metastasis. In the future, we will conduct prospective studies to solve this problem. Second, one potentially important factor not taken into account in our study is follow-up and recurrence data, which

was lacking in our study. Third, to avoid the mutual influence between the multiple lesions, this study only included PTC patients with a single lesion. In the future, we will include patients with multiple bilateral lesions for more in-depth research. To sum up, a multicenter, larger sample, and prospective clinical trials should be performed to identify the predicting factors of LLNM in patients with PTC and provide more supporting evidence with greater reliability.

Conclusion

We demonstrated that DECT quantitative parameters and thyroid functional indicators could effectively predict ipsi-LLNM in patients with PTC. This strategy may be an effective assist for clinicians to accurately formulate surgical procedures before surgery. With further verification in a larger population and prospective research, our result has great potential to serve as an important decision support tool in clinical applications.

Abbreviations

CLND = central cervical lymph nodes dissection

CLNM = central cervical lymph nodes metastasis

DECT = dual-energy CT

ETE = extrathyroidal extension

IC = iodine concentration

ICC = intraclass correlation coefficient

LNM = lymph nodes metastasis

LLND = lateral cervical lymph nodes dissection

LLNM = lateral cervical lymph nodes metastasis

NIC = normalized iodine concentration

PTC = papillary thyroid carcinoma

RAI = radioactive iodine

Declarations

Ethics approval and consent to participate: This retrospective study was approved by the ethics committee of Tianjin First Central Hospital (2019N153KY), and the requirement for written informed

consent was waived since the retrospective nature.

Consent for publication: Not applicable

Availability of data and materials: The data that support the findings of this study are available from Tianjin First Central Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the corresponding authors upon reasonable request and with permission of Tianjin First Central Hospital.

Competing interests: The authors declare that they have no competing interests.

Funding: No

Authors' contributions:

YZ: design experiment, perform research, analyze data and make relevant statistics, draft the manuscript and make repeated modifications

HZ: Participate in experimental design, analyze data and make relevant statistics, complete part of the manuscript revision work

WL: analyze data and make relevant statistics

YG: revised the manuscript several times, language polishing

FS: acquisition parameters, participate in research

YS: acquisition parameters, make relevant statistics

YG: acquisition parameters, data measurement

XL: acquisition parameters, data measurement

WW: active communication with the clinic, revised the manuscript

SX: design experiment, critically review the intellectual content of the manuscript, financial support for research, full guidance

All authors read and approved the final manuscript.

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Tables

Table 1: Baseline information and DECT images characteristics of PTC patients

	Total (n=406)	LLNM (-) (n=278)	LLNM (+) (n=128)	*P* value
Age*				.179
≤ 55	283 (69.7)	188 (67.6)	95 (74.2)	
> 55	123 (30.3)	90 (32.4)	33 (25.8)	
Sex, n (%)				.146
Female	322 (79.3)	226 (70.2)	96 (29.8)	
Male	84 (20.7)	52 (61.9)	32 (38.1)	
Location				.493
Left lobe	189 (46.6)	127 (67.2)	62 (32.8)	
Right lobe	193 (47.5)	132 (68.4)	61 (31.6)	
Isthmus	24 (5.9)	19 (79.2)	5 (20.8)	
HT, n (%)				.270
Negative	323 (79.6)	217(67.2)	106 (32.8)	
Positive	83 (20.4)	61 (73.5)	22 (26.5)	
Nodular Goiter, n (%)				.940
Negative	277 (68.2)	190 (68.6)	87 (31.4)	
Positive	129 (31.8)	88 (68.2)	41 (31.8)	
Cystic degeneration				.047
Negative	257 (63.3)	215 (83.7)	42 (16.3)	
Positive	149 (36.7)	63 (42.3)	86 (57.7)	
Calcification				.000
Negative	321 (79.0)	257 (80.1)	64 (19.9)	
Positive	85(21.0)	21 (24.7)	64 (75.3)	
ETE				.000
Negative	302 (74.4)	268 (88.7)	34 (11.3)	
Positive	104 (25.6)	10 (9.6)	94 (90.4)	

* We divided the patients into two groups based on age using 55-year-old as cut-off value according to the 8th AJCC staging systems.

DECT = dual-energy CT, PTC = papillary thyroid carcinoma, LLNM = lateral cervical lymph node metastasis, ETE = extrathyroidal extension

Table 2: DECT parameters and thyroid functional indicators in patients with PTC

	Total (n=406)	LLNM (-) (n=278)	LLNM (+) (n=128)	*P* value
Tg (ng/ml)	25.54 (12.08-134.12)	16.28 (9.55-35.46)	149.26 (104.05-182.76)	< .0001*
Anti-Tg (IU/ml)	11.5 (7.70-110.02)	7.70 (7.70-19.21)	117.70 (13.50-166.40)	< .0001*
Anti-TPO (IU/ml)	7.01 (3.31-18.12)	5.24 (1.52-10.70)	19.94 (3.70-156.56)	< .0001*
Volume (cm^3)	0.38 (0.14-1.44)	0.18 (0.01-0.70)	0.72 (0.18-2.76)	.000†
IC IAP (mg/ml)	3.0 (2.6-3.7)	2.8 (2.4-3.2)	3.8 (3.3-4.5)	.000†
IC IVP (mg/ml)	2.8 (2.4-3.3)	2.6 (2.2-3.1)	3.3 (2.8-4.1)	.000†

*: Mann-Whitney U test, median (IQR)

DECT = dual-energy CT, PTC = papillary thyroid carcinoma, LLNM = lateral lymph node metastasis, IC = iodine concentration, IAP = in arterial phase, IVP = in venous phase, IQR = interquartile range

Table 3: Risk factors for ipsi-LLNM in patients with PTC

	Univariate analysis			Mutivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Sex	0.690	0.484-1.341	.147			
Age	0.726	0.454-1.160	.180			
Tg (ng/ml)	2.832	1.837-4.365	.000	2.668	1.590-4.475	.000
Anti-Tg (IU/ml)	2.121	1.386-3.245	.001	2.001	1.202-3.333	.008
Anti-TPO (IU/ml)	1.054	0.693-1.603	.805			
HT	0.738	0.430-1.267	.271			
Nodular goiter	1.018	0.649-1.594	.940			
Volume (cm^3)	1.093	1.029-1.161	.004			
Cystic degeneration	1.816	1.190-2.771	.006			
Calcification	1.989	1.298-3.048	.002			
ETE	6.350	4.012-10.050	.000	6.335	3.768-10.651	.000
IC IAP (mg/ml)	4.418	2.787-7.004	.000	3.691	2.170-6.278	.000
IC IVP (mg/ml)	2.517	1.640-3.863	.000	2.122	1.271-3.541	.004

LLNM = lateral lymph node metastasis, PTC = papillary thyroid carcinoma, OR = odds ratio, CI = confidence interval, HT = Hashimoto's thyroiditis, ETE = extrathyroidal extension, IC = iodine concentration, IAP = in arterial phase, IVP = in venous phase

Table 4: Prediction of each parameter for ipsi-LLNM in patients with PTC

Parameters	Cut-off value	AUC (95%CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*P* Value
Tg (ng/ml)	> 100.01	0.856 (0.818, 0.889)	76.56 (68.3, 83.6)	88.85 (84.5, 92.3)	76.0 (69.1, 81.7)	89.2 (85.7, 91.9)	< .0001
Anti-Tg (IU/ml)	> 89.43	0.766 (0.721, 0.806)	71.09 (62.4, 78.8)	86.33 (81.7, 90.1)	70.5 (63.6, 76.7)	86.6 (83.1, 89.5)	< .0001
ETE	N/A	0.713 (0.667, 0.757)	66.41 (57.5, 74.5)	76.26 (70.8, 81.1)	56.3 (50.2, 62.2)	83.1 (79.3, 86.4)	< .0001
IC IAP (mg/ml)	> 3.4	0.846 (0.807, 0.879)	72.66 (64.1, 80.2)	85.97 (81.3, 89.8)	70.5 (63.6. 76.5)	87.2 (83.7, 90.1)	< .0001
IC IVP (mg/ml)	> 3.1	0.777 (0.733, 0.816)	53.91 (44.9, 62.8)	91.37 (87.4, 94.4)	74.2 (65.5, 81.3)	81.2 (78.1, 83.9)	< .0001

* Data in parentheses are 95% confidence intervals (CIs).

LLNM = lateral lymph nodes metastasis, PTC = papillary thyroid carcinoma, AUC = area under the curve, PPV = positive predictive value, NPV = negative predictive value, ETE = extrathyroidal extension, IC = iodine concentration, IAP = in arterial phase, IVP = in venous phase

Figures

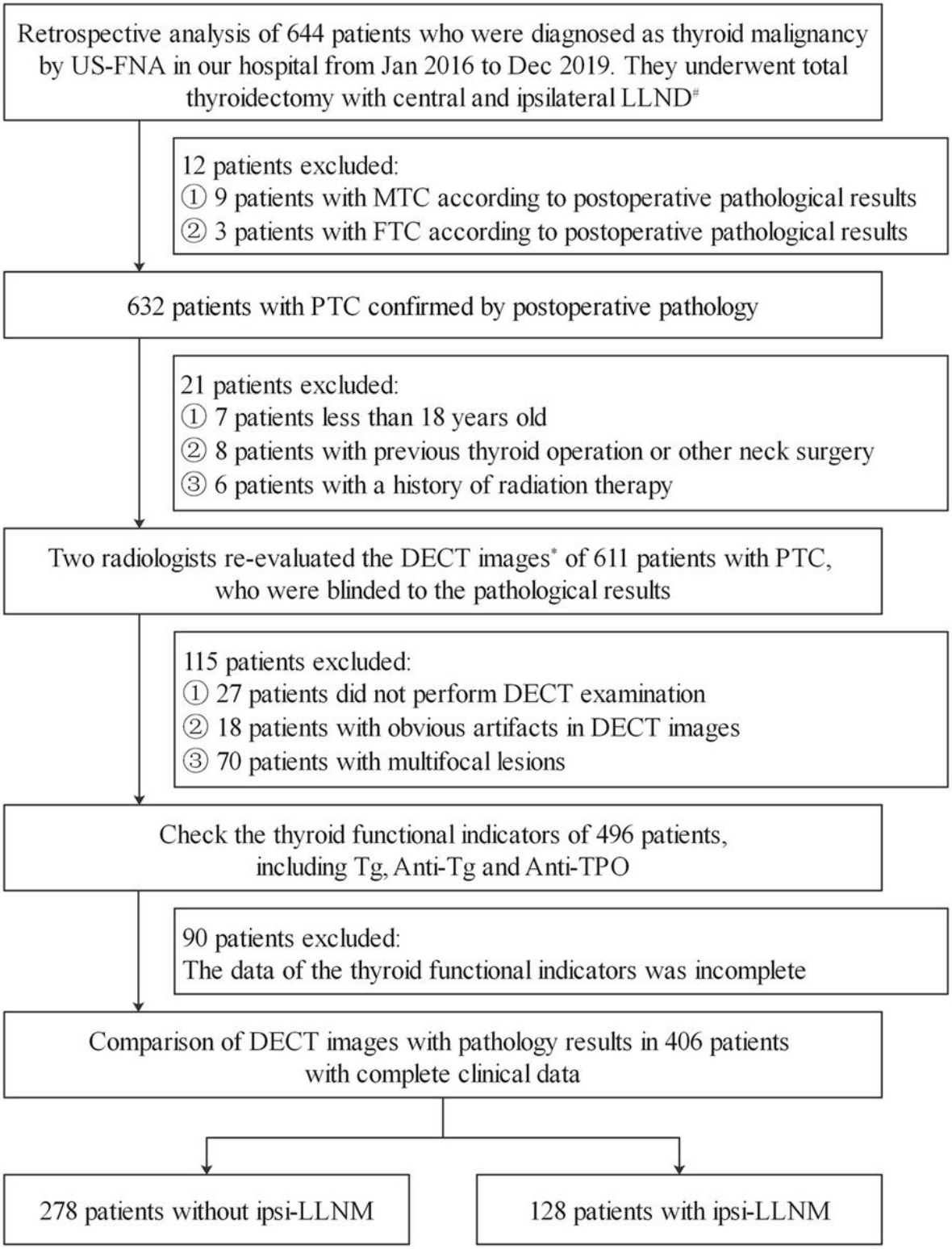

Figure 1

Flowchart showed criteria of inclusion and exclusion of patients with PTC in the current study. # According to ATA guidelines, patients with suspected LNM in the central and lateral cervical regions based on preoperative US and/or DECT examination would undergo total thyroidectomy and cervical lymph node dissection. * Patients who were suspected of thyroid carcinoma with LNM by US were initially selected and underwent DECT to determine the extent of LNM before operation. US = ultrasound,

FNA = fine-needle aspiration, MTC = medullary thyroid carcinoma, FTC = follicular thyroid carcinoma, PTC = papillary thyroid carcinoma, DECT = dual-energy computed tomography, LLNM = lateral cervical lymph node metastasis, ATA = American Thyroid Association, LNM = lymph node metastasis

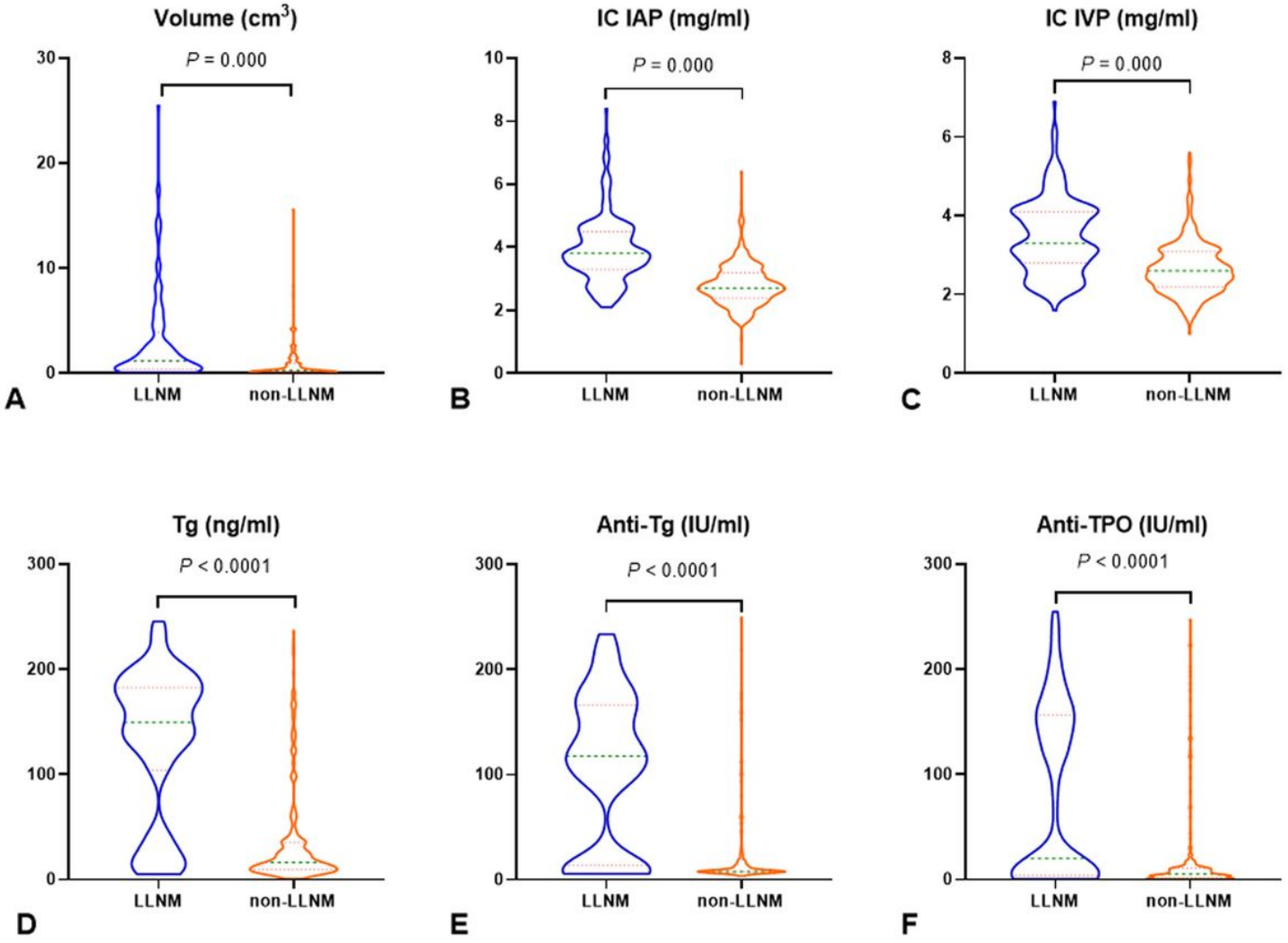

Figure 2

Violin plot showed that volume (A), IC in arterial phase (B), IC in venous phase (C), Tg (D), Anti-Tg (E) and Anti-TPO (F) were statistically significant in predicting non-LLNM and LLNM. LLNM = lateral lymph node metastasis, IC = iodine concentration, IAP = in arterial phase, IVP = in venous phase

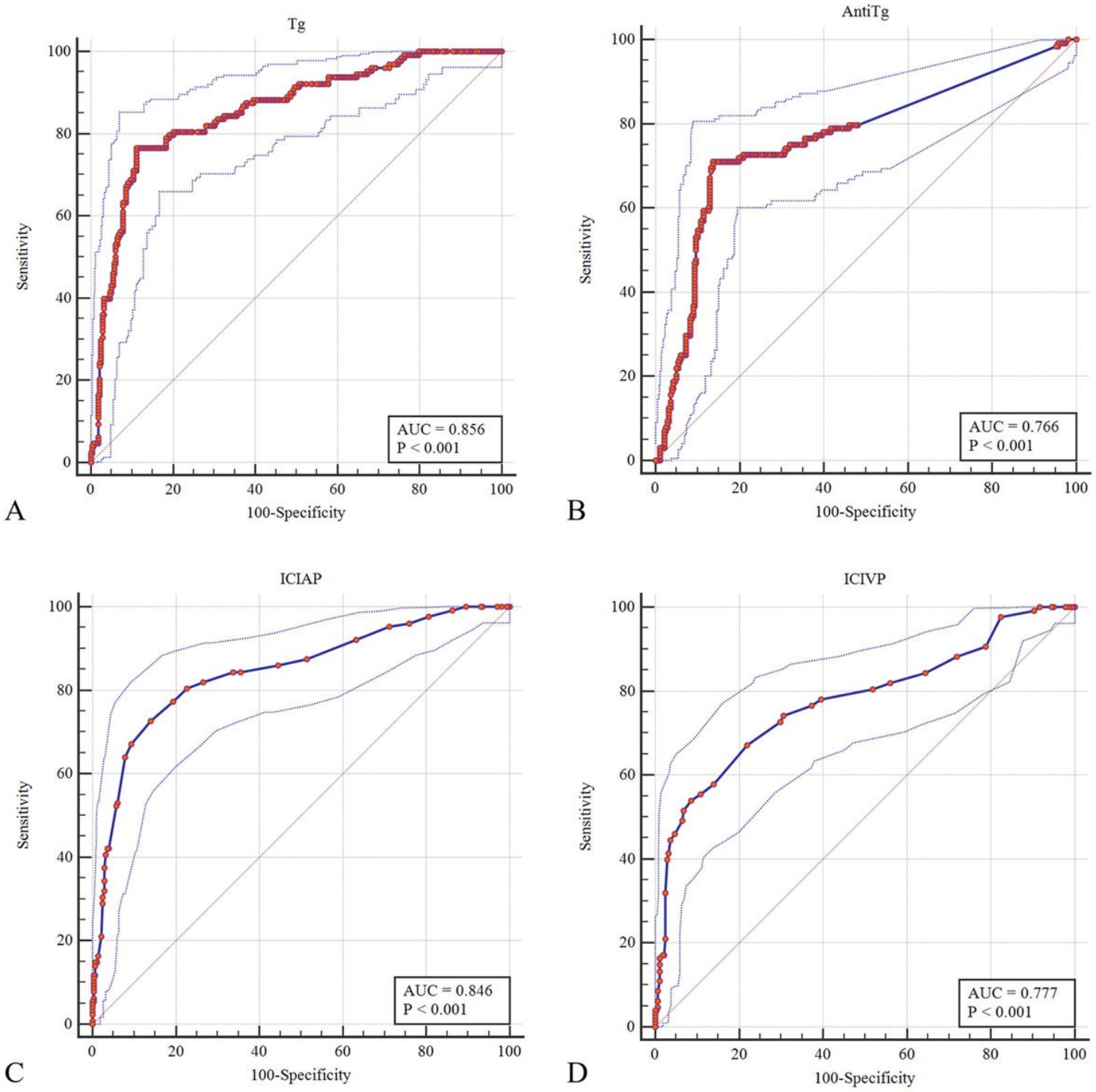

Figure 3

ROC curves of DECT parameters and thyroid functional indicators in patients with PTC. A, AUC, sensitivity and specificity of Tg were 0.856 76.56% and 88.85%, respectively, with cut-off value of 100.01 ng/ml. B, AUC, sensitivity and specificity of Anti-Tg were 0.766, 71.09% and 86.33%, respectively, with cut-off value of 89.43 IU/ml. C, AUC, sensitivity and specificity of IC IAP were 0.846, 72.66% and 85.97%, respectively, with cut-off value of 3.4 mg/ml. D, AUC, sensitivity and specificity of IC IVP were 0.777, 53.91% and 91.37%, respectively, with cut-off value of 3.1 mg/ml. ROC = receiver operating characteristic, DECT =

dual-energy computed tomography, AUC = area under the curve, IC = iodine concentration, IAP = in arterial phase, IVP = in venous phase

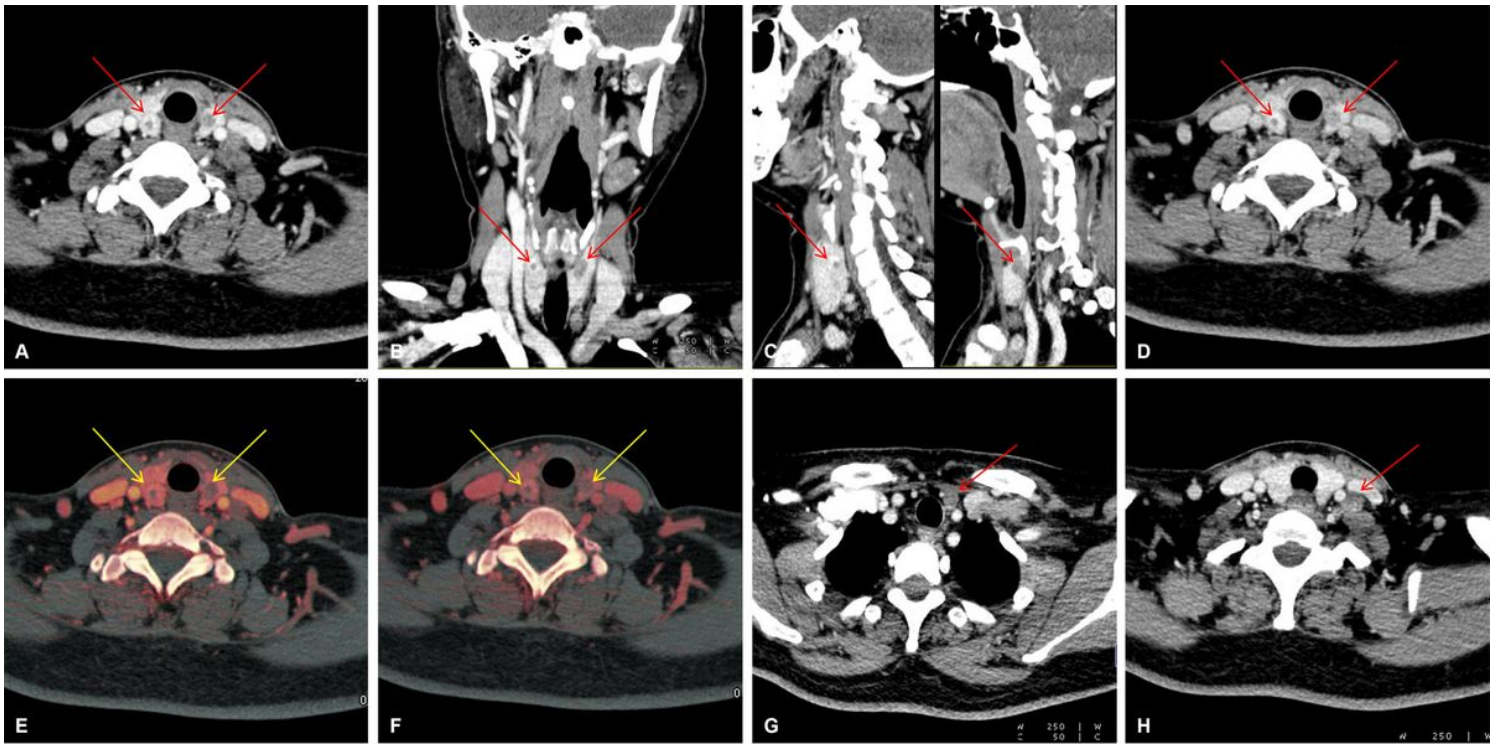

Figure 4

Female, 48 years old. Total thyroidectomy and bilateral lateral level Ⅱ-Ⅴ dissection was performed. Pathology confirmed papillary thyroid microcarcinoma of bilateral lobes with a diameter 0.7 cm (R) and 1.1 cm (L). 6, 4, 4 and 5 metastatic lymph nodes were found in the right level Ⅱ, Ⅲ, left level Ⅱ and Ⅲ. Two small nodules were found in left and right lobes of thyroid on contrast-enhanced arterial phase (red arrow, A, B and C) and venous phase (red arrow, D). Both lesions located in superior poles of thyroid (red arrow, B) and showed heterogeneous enhancement. The lesion in the left lobe partially penetrated through the capsule (red arrow, A, B, C). Primary foci were found in iodine map in arterial phase (yellow arrow, E, IC of right lesion, 5.5 mg/ml; IC of left lesion, 3.5 mg/ml) and in venous phase (yellow arrow, F, IC of right lesion, 3.7 mg/ml; IC of left lesion, 2.9 mg/ml). Enlarged lymph nodes located in left level Ⅱb (G) and left level Ⅱa (H) were found in arterial phase. IC = iodine concentration

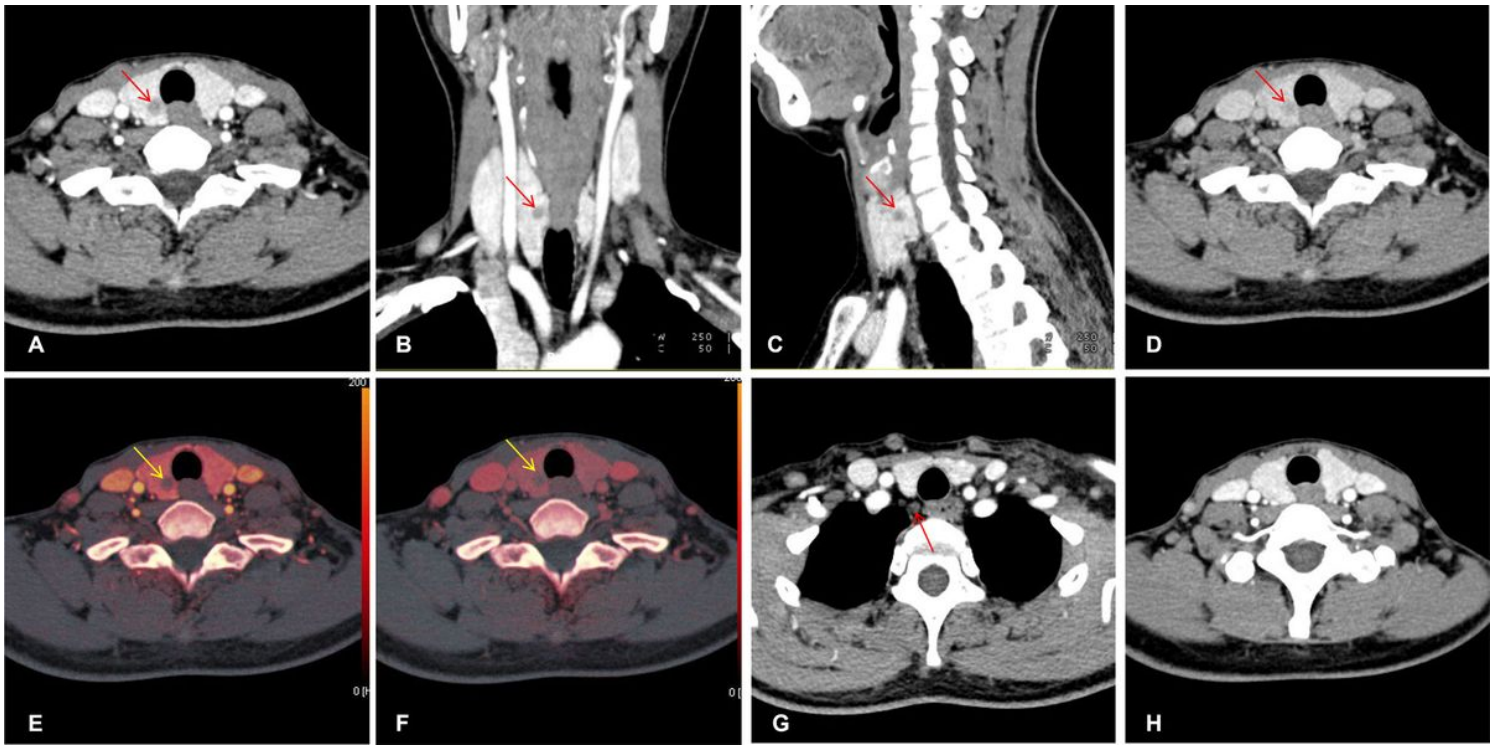

Figure 5

Male, 38 years old. Right lobe of thyroid and isthmus with functional right level Ⅵ dissection was performed. Pathology confirmed papillary thyroid microcarcinoma of right lobe with a diameter 0.9 cm, which was accompanied by Hashimoto's thyroiditis. No metastatic lymph nodes were found in the right level Ⅵ. One small nodule was found in right lobe of thyroid on contrast-enhanced arterial phase (red arrow, A, B, C) and venous phase (red arrow, D). The lesion located in the middle of thyroid (red arrow, B) and showed homogeneous enhancement. Primary focus was found in iodine map in arterial phase (yellow arrow, E, IC of the lesion, 1.1 mg/ml) and in venous phase (yellow arrow, F, IC of the lesion, 1.0 mg/ml). One benign lymph node located in right level Ⅱb (G) was found in arterial phase. No metastatic lymph nodes were found in lateral level Ⅰ-Ⅲ (H). IC = iodine concentration

Supplementary Files

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