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

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Research article

Keywords: Papillary thyroid carcinoma, Lateral lymph nodes metastasis, Dual-energy computed tomography, Iodine concentration, Tg, Anti-Tg, Extrathyroidal extension

DOI: https://doi.org/10.21203/rs.3.rs-115861/v1

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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 $\lambda_{\text{HU}}$ 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 Definition 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 mm² 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 \( (P \text{ range } .000 - .006) \). Further multivariable logistic regression analysis showed that among these parameters, Tg \( \left( \text{OR} = 2.668; 95\% \text{CI: } 1.590, 4.475; P .000 \right) \), Anti-Tg \( \left( \text{OR} = 2.001; 95\% \text{CI: } 1.202, 3.333; P .008 \right) \), ETE \( \left( \text{OR} = 6.335; 95\% \text{CI: } 3.768, 10.651; P .000 \right) \), IC in arterial phase \( \left( \text{OR} = 3.691; 95\% \text{CI: } 2.170, 6.278; P .000 \right) \) and IC in venous phase \( \left( \text{OR} = 2.122; 95\% \text{CI: } 1.271, 3.541; P .004 \right) \) 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 \( \left( \text{AUC 0.856, 95\%CI 0.818-0.889} \right) \), 89.43 IU/ml \( \left( \text{AUC 0.766, 95\%CI 0.721-0.806} \right) \), 3.4 mg/ml \( \left( \text{AUC 0.846, 95\%CI 0.807-0.879} \right) \) and 3.1 mg/ml \( \left( \text{AUC 0.777, 95\%CI 0.733-0.816} \right) \), 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 \( > 3.4 \text{mg/ml} \) and IC in the venous phase \( > 3.1 \text{mg/ml} \) of primary lesions were positively associated with the risk of ipsi-LLNM in patients with PTC. Second, Tg \( > 100.01 \text{ng/ml} \) and Anti-Tg \( > 89.43 \text{IU/ml} \) 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 micrometastasis. 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.

**Acknowledgements:** The authors thank Jianhua Gu, MD, of Department of General Surgery, Tianjin First Central Hospital for patient recruitment and guidance of clinical work; Wen Shen, MD, of Department of Radiology, Tianjin First Central Hospital for image acquisition; Xi Zhao, Senior engineer, of Siemens for his support for dual-energy CT image post-processing.
References

1. Carlson RW. The NCCN 2019 Annual Conference: Improving the Quality, Effectiveness, and Efficiency of Cancer Care. Journal of the National Comprehensive Cancer Network : JNCCN. 2019;17(5.5):529-30.

2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: a cancer journal for clinicians. 2019;69(1):7-34.

3. McLeod DS, Sawka AM, Cooper DS. Controversies in primary treatment of low-risk papillary thyroid cancer. Lancet (London, England). 2013;381(9871):1046-57.

4. Raffaelli M, De Crea C, Sessa L, Fadda G, Lombardi CP, Bellantone R. Risk factors for central neck lymph node metastases in follicular variant vs. classic papillary thyroid carcinoma. Endocrine. 2018;62(1):64-70.

5. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid : official journal of the American Thyroid Association. 2016;26(1):1-133.

6. Oh HS, Kwon H, Song E, Jeon MJ, Song DE, Kim TY, et al. Preoperative Clinical and Sonographic Predictors for Lateral Cervical Lymph Node Metastases in Sporadic Medullary Thyroid Carcinoma. Thyroid : official journal of the American Thyroid Association. 2018;28(3):362-8.

7. Yeh MW, Bauer AJ, Bernet VA, Ferris RL, Loevner LA, Mandel SJ, et al. American Thyroid Association statement on preoperative imaging for thyroid cancer surgery. Thyroid : official journal of the American Thyroid Association. 2015;25(1):3-14.

8. Khokhar MT, Day KM, Sangal RB, Ahmedli NN, Pisharodi LR, Beland MD, et al. Preoperative High-Resolution Ultrasound for the Assessment of Malignant Central Compartment Lymph Nodes in Papillary Thyroid Cancer. Thyroid : official journal of the American Thyroid Association. 2015;25(12):1351-4.

9. Xu JM, Xu XH, Xu HX, Zhang YF, Guo LH, Liu LN, et al. Prediction of cervical lymph node metastasis in patients with papillary thyroid cancer using combined conventional ultrasound, strain elastography, and acoustic radiation force impulse (ARFI) elastography. European radiology. 2016;26(8):2611-22.

10. Chang W, Tang L, Lu C, Wu M, Chen M. Shear wave elastography in the evaluation of level VI lymph nodes in papillary thyroid carcinoma: combined with gray-scale ultrasound ex vivo. BMC Cancer. 2018;18(1):1001.

11. Han Z, Lei Z, Li M, Luo D, Ding J. Differential diagnosis value of the ultrasound gray scale ratio for papillary thyroid microcarcinomas and micronodular goiters. Quantitative imaging in medicine and surgery. 2018;8(5):507-13.
12. Cho SJ, Suh CH, Baek JH, Chung SR, Choi YJ, Lee JH. Diagnostic performance of CT in detection of metastatic cervical lymph nodes in patients with thyroid cancer: a systematic review and meta-analysis. European radiology. 2019;29(9):4635-47.

13. Debnam JM, Guha-Thakurta N, Sun J, Wei W, Zafereo ME, Cabanillas ME, et al. Distinguishing Recurrent Thyroid Cancer from Residual Nonmalignant Thyroid Tissue Using Multiphasic Multidetector CT. AJNR American journal of neuroradiology. 2020;41(5):844-51.

14. Zhou Y, Su GY, Hu H, Ge YQ, Si Y, Shen MP, et al. Radiomics analysis of dual-energy CT-derived iodine maps for diagnosing metastatic cervical lymph nodes in patients with papillary thyroid cancer. European radiology. 2020.

15. Lee JH, Ha EJ, Kim JH. Application of deep learning to the diagnosis of cervical lymph node metastasis from thyroid cancer with CT. European radiology. 2019.

16. Park JE, Lee JH, Ryu KH, Park HS, Chung MS, Kim HW, et al. Improved Diagnostic Accuracy Using Arterial Phase CT for Lateral Cervical Lymph Node Metastasis from Papillary Thyroid Cancer. AJNR American journal of neuroradiology. 2017;38(4):782-8.

17. Liu X, Ouyang D, Li H, Zhang R, Lv Y, Yang A, et al. Papillary thyroid cancer: dual-energy spectral CT quantitative parameters for preoperative diagnosis of metastasis to the cervical lymph nodes. Radiology. 2015;275(1):167-76.

18. Lu W, Zhong L, Dong D, Fang M, Dai Q, Leng S, et al. Radiomic analysis for preoperative prediction of cervical lymph node metastasis in patients with papillary thyroid carcinoma. European journal of radiology. 2019;118:231-8.

19. Li C, Yu W, Fan J, Li G, Tao X, Feng Y, et al. Thyroid functional parameters and correlative autoantibodies as prognostic factors for differentiated thyroid cancers. Oncotarget. 2016;7(31):49930-8.

20. Golbert L, de Cristo AP, Faccin CS, Farenzena M, Folgieri H, Graudenz MS, et al. Serum TSH levels as a predictor of malignancy in thyroid nodules: A prospective study. PloS one. 2017;12(11):e0188123.

21. Sahin AA, Gilligan TD, Caudell JJ. Challenges With the 8th Edition of the AJCC Cancer Staging Manual for Breast, Testicular, and Head and Neck Cancers. Journal of the National Comprehensive Cancer Network : JNCCN. 2019;17(5.5):560-4.

22. Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for persistent/recurrent and metastatic differentiated thyroid cancer 2018 (English version). Chin J Cancer Res. 2019;31(1):99-116.

23. Nixon IJ, Wang LY, Migliacci JC, Eskander A, Campbell MJ, Aniss A, et al. An International Multi-Institutional Validation of Age 55 Years as a Cutoff for Risk Stratification in the AJCC/UICC Staging System for Well-Differentiated Thyroid Cancer. Thyroid : official journal of the American Thyroid Association. 2016;26(3):373-80.

24. Han K, Song K, Choi BW. How to Develop, Validate, and Compare Clinical Prediction Models Involving Radiological Parameters: Study Design and Statistical Methods. Korean journal of radiology.
25. Haugen BR. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: What is new and what has changed? Cancer. 2017;123(3):372-81.

26. Lee DH, Lee YH, Seo HS, Lee KY, Suh SI, Ryoo I, et al. Dual-energy CT iodine quantification for characterizing focal thyroid lesions. Head & neck. 2019;41(4):1024-31.

27. Tawk AM, Michael Bucher A, Vogl TJ. Dual-Energy Computed Tomography Applications for the Evaluation of Cervical Lymphadenopathy. Neuroimaging clinics of North America. 2017;27(3):461-8.

28. Groen AH, Klein Hesslink MS, Plukker JT, Sluiter WJ, van der Horst-Schrivers AN, Brouwers AH, et al. Additional value of a high sensitive thyroglobulin assay in the follow-up of patients with differentiated thyroid carcinoma. Clinical endocrinology. 2017;86(3):419-24.

29. Nabhan F, Porter K, Senter L, Ringel MD. Anti-thyroglobulin antibodies do not significantly increase the risk of finding iodine avid metastases on post-radioactive iodine ablation scan in low-risk thyroid cancer patients. Journal of endocrinological investigation. 2017;40(9):1015-21.

30. Al-Rabia MW. Correlation of thyroid antibodies with TSH, T3 and T4 hormones in patients diagnosed with autoimmune thyroid disorders. Pakistan journal of pharmaceutical sciences. 2017;30(2(Suppl.)):607-12.

31. Chao Li WY, Jinchuan Fan, Guojun Li, Xiaofeng Tao, Yun Feng, Ronghao Sun. Thyroglobulin Antibody Is Associated with Increased Cancer Risk in Thyroid Nodules. Oncotarget. 2016;7(31):9.

32. Sun RH, Li C, Zhou YQ, Cai YC, Shui CY, Liu W, et al. Predictive role of intraoperative clinicopathological features of the central compartment in estimating lymph nodes metastasis status. Annals of translational medicine. 2019;7(18):471.

33. Heng Y, Yang Z, Zhou L, Lin J, Cai W, Tao L. Risk stratification for lateral involvement in papillary thyroid carcinoma patients with central lymph node metastasis. Endocrine. 2020.

34. Back K, Kim JS, Kim JH, Choe JH. Superior Located Papillary Thyroid Microcarcinoma is a Risk Factor for Lateral Lymph Node Metastasis. Annals of surgical oncology. 2019;26(12):3992-4001.

35. Siddiqui S, White MG, Antic T, Grogan RH, Angelos P, Kaplan EL, et al. Clinical and Pathologic Predictors of Lymph Node Metastasis and Recurrence in Papillary Thyroid Microcarcinoma. Thyroid : official journal of the American Thyroid Association. 2016;26(6):807-15.

36. Kim SK, Park I, Woo JW, Lee JH, Choe JH, Kim JH, et al. Predictive Factors for Lymph Node Metastasis in Papillary Thyroid Microcarcinoma. Annals of surgical oncology. 2016;23(9):2866-73.

37. Kim K, Zheng X, Kim JK, Lee CR, Kang SW, Lee J, et al. The contributing factors for lateral neck lymph node metastasis in papillary thyroid microcarcinoma (PTMC). Endocrine. 2020.

38. Qiu Y, Fei Y, Liu J, Liu C, He X, Zhu N, et al. Prevalence, Risk Factors And Location Of Skip Metastasis In Papillary Thyroid Carcinoma: A Systematic Review And Meta-Analysis. Cancer Manag Res. 2019;11:8721-30.
39. Zhao H, Huang T, Li H. Risk factors for skip metastasis and lateral lymph node metastasis of papillary thyroid cancer. Surgery. 2019;166(1):55-60.

40. Liu C, Xiao C, Chen J, Li X, Feng Z, Gao Q, et al. Risk factor analysis for predicting cervical lymph node metastasis in papillary thyroid carcinoma: a study of 966 patients. BMC Cancer. 2019;19(1):622.

41. Nie X, Tan Z, Ge M. Skip metastasis in papillary thyroid carcinoma is difficult to predict in clinical practice. BMC Cancer. 2017;17(1):702.

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.
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 (cm³)         | 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)

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

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

| Parameter                  | 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 (cm³)               | 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
| 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