# RISK-BENEFIT CONSIDERATIONS AND STAGING OF DIFFERENTIATED THYROID CANCER

EDITED BY: Valentina Drozd and Christoph Reiners
PUBLISHED IN: Frontiers in Endocrinology

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88971-737-8
DOI 10.3389/978-2-88971-737-8

## About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

## Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

## Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

## What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

# RISK-BENEFIT CONSIDERATIONS AND STAGING OF DIFFERENTIATED THYROID CANCER

Topic Editors:
**Valentina Drozd,** Other, Belarus
**Christoph Reiners,** University Hospital Würzburg, Germany

**Citation:** Drozd, V., Reiners, C., eds. (2021). Risk-benefit Considerations and Staging of Differentiated Thyroid Cancer. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88971-737-8

# Table of Contents

frontiers in Endocrinology

EDITORIAL
published: 08 October 2021
doi: 10.3389/fendo.2021.755323

# Editorial: Differentiated Thyroid Cancer - Risk Adapted Therapy, Genetic Profiling and Clinical Staging

*Christoph Reiners*[1]* *and Valentina M. Drozd*[2]

[1] Department of Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany, [2] International Foundation "Arnica", Minsk, Belarus

**Keywords: differentiated thyroid cancer, risk adapted therapy, genetic profiling, staging of the primary, staging of lymph nodes**

**Editorial on the Research Topic**

**Risk-Benefit Considerations and Staging of Differentiated Thyroid Cancer**

OPEN ACCESS

***Edited and reviewed by:***
*Terry Francis Davies, Icahn School of Medicine at Mount Sinai, United States*

***Correspondence:**
*Christoph Reiners*
*reiners_c@ukw.de*

***Specialty section:***
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

***Received:*** *08 August 2021*
***Accepted:*** *27 August 2021*
***Published:*** *08 October 2021*

***Citation:***
*Reiners C and Drozd VM (2021) Editorial: Differentiated Thyroid Cancer - Risk Adapted Therapy, Genetic Profiling and Clinical Staging. Front. Endocrinol. 12:755323. doi: 10.3389/fendo.2021.755323*

## INTRODUCTION

The incidence of differentiated thyroid cancer (DTC) has steadily increased since the 1980´s (1, 2). This highly significant rise is thought to be primarily due to the increasing use of thyroid ultrasound screening leading to overdiagnosis and overtreatment of early stage papillary thyroid microcancers (microPTC) (3, 4). In contrast with the steep increases observed for incidence, long-term DTC mortality, being generally low, declined or stabilized in many countries worldwide during over two or three decades. Guidelines today, recommend non-aggressive treatment for early stage microPTC (5) or even active surveillance only, based on positive experiences made with this concept in Japan (6).

However, not all cancer registries worldwide recorded a significant increase of only small, early-stage tumours but a rise of larger, later-stage tumours too (1, 2, 7), which is contrary to the idea of the dominant impact of screening (8). In addition, in North America, Australia and Asia, the downward trend of thyroid cancer mortality levels off or slightly increases since around 2000 (1, 2). So not all thyroid cancers can be considered as "indolent" or "harmless" (8) and the challenge is to make decisions for therapy based on proper differentiation between low, intermediate and high-risk thyroid cancers which may be difficult even in small DTC (9).

Fifteen papers in this Research Topic address important questions, which have to be answered if the approach of "personalized" or "precision" medicine, which today is generally accepted, shall be applied to DTC too.

Very relevant issues to be solved relate to risk-benefit considerations covering a broad spectrum from small, non-aggressive papillary thyroid cancers (PTC) in young patients, to aggressive, metastasizing cancers in elderly people.

## Early Diagnosis - Risk Adapted Therapy

Krajewska et al., Gliwice Poland contribute a comprehensive review on: "Early diagnosis of low-risk papillary thyroid cancer results rather in overtreatment than a better survival" with more than 100 references. The main message of this paper is that there is overdiagnosis in (very) early stages of PTC cases stage pT1 worldwide, which need not be treated aggressively - if at all. But – on the contrary – the increasing detection of more advanced cases of PTC demands adequate treatment. Benefits and side effects of surgical therapy, I-131 treatment and thyroid hormone supplementation should be carefully considered. Finally, the authors state that "numerous clinical trials are needed to change the clinical management of low and intermediate risk PTC".

Concerning the other side of the spectrum of DTC's aggressiveness, Qiu et al. from Shanghai, China, present a paper on "Long-term Outcomes and Prognoses of Elderly Patients (≥65-years-old) with Distant Metastases from Well-differentiated Thyroid Cancer during Radioiodine Therapy and Follow-up". In a study of 193 DTC patients ≥ 65 years of age, distant metastases are prevalent in 31% of the cases, which were followed-up for up to 24 years. The 5 and 10 year disease specific survival is reported to be 77% and 49% respectively. Gross thyroidal extension and I-131 responsiveness could be identified to be significant, independent prognostic indicators, thus confirming the effectiveness of radioiodine therapy (RIT) in patients with advanced thyroid cancer.

## Genetic Risk Stratification

To decide properly which treatment should be recommended to a given patient, it is necessary to stage the tumour properly and to assign this clinical stage to defined risk categories. This today should be done including appropriate instruments of genetic profiling. Zhao et al., Hangzhou China present "Identification of A Prognostic 3-Gene Risk Prediction Model for Thyroid Cancer" using 506 DTC samples and 56 controls from the TCGA cancer genome database. Using receiver operator characteristics (ROC) to test predictability of 3-year survival, the area under the curve (AUC) corresponds remarkably to 0.85 for the 3 gene model with GHR, GPR125 and AtP2c2 versus AUC´s of 0.79-0.84 for single genes. GHR is a gene coding for transmembrane receptors of growth hormone, GPR125 promotes cell adhesion and AtP2c2 is a calcium transport coding gene.

Similarly, Xie et al. from Shenyang, China, used the same TCGA database for "Analysis of the prognostic value and potential molecular mechanisms of TREM-1 overexpression in papillary thyroid cancer *via* bioinformatics methods". They focus on the triggering receptor expressed on myeloid cells-1 (TREM-1) described as biomarker in many cancers, but not up to now in thyroid cancer. Genes co-expressed with TREM-1 participate in immune related pathways. Xie et al. identified TREM-1 expression to be correlated with immune infiltration, tumour progression, and poor overall survival, with an AUC of 0.84. These interesting results obtained with bioinformatics methods have to be confirmed with much larger samples and experimental research.

## Staging the Primary, Uni Versus Bilateral PTC

PTCs are frequently diagnosed by chance if a non-suspicious nodule is surgically resected or lobectomy is performed for non-oncological reasons. In this case it is of utmost importance to know if the cancer disease is restricted to the lobe surgically resected or if possibly the contralateral lobe is affected too.

Feng et al., Changzhou, China, present a study on "Management of Clinically Solitary Papillary Thyroid Carcinoma Patients According to Risk-scoring Model for Contralateral Occult Carcinoma" in which 573 clinically solitary PTC patients undergo lobectomy, identifying 3.7% ipsilateral and 15,5% contralateral occult cancers with their approach. The 10-point risk scoring model for contralateral cancer includes the points "benign nodule (point-load 2)", "tumour size > 1cm (load 1)", "extrathyroidal extension (load 3)", "central LN-metastases (load 2)", "lateral LN-metastases (load 2)", the ROC area under the curve amounting to 0.91 for a cut-off of 3.5 summarized points.

Zhang et al., Shenyang, China, contribute to the same Research Topic with a paper on "Risk Factors for Contralateral Occult Carcinoma in Patients with Unilateral Papillary Thyroid Carcinoma: A Retrospective Study and Meta-Analysis". The meta-analysis in 4,347 patients includes 26% occult contralateral cancers. Significant risk factors are "tumour size > 1cm" with an odds ratio (OR) of 2.16, "central neck lymph node metastases" OR 2.80 and "multifocality ipsilateral" OR 5.62. Sex, age, ETE, capsular invasion, Hashimoto´s disease and lateral lymph node metastases are not described as risk factors for contralateral occult carcinoma.

## Staging the Lymph Nodes

Today's guidelines for treatment of early-stage DTC (5, 10) strongly rely on lymph node staging. In this context it is important to use up-to-date diagnostic procedures like Colour-Doppler, or Contrast-Enhanced-Ultrasound. Eight papers of this section address multiparameter approaches to predict lymph node metastases (LNM) in different anatomic locations of the neck.

"Predictive factors of lymph node metastasis in patients with papillary microcarcinoma of the thyroid: a retrospective analysis on 293 cases" is the title of a paper by Medas et al. from Cagliari, Italy. An incidence of 13.7% of LNM (in any location) is described in their single hospital study in 293 PTC patients. Independent risk factors are: "age < 45", "tumour size > 6 mm", "tall cell variant", "extrathyroidal extension (ETE)" and "angioinvasion". The authors conclude that "size of the tumour being the most significant predictive factor" and that "smaller size of the tumour should be considered for active surveillance strategies".

Two papers focus on preoperative prediction of central lymph node metastases. Chen et al. from Changsha, China, describe "Sonographic characteristics of papillary thyroid carcinoma with coexistent Hashimoto's thyroiditis in the preoperative prediction of central lymph node metastasis". They report a single hospital study of 177 patients with histologically verified PTC and Hashimoto Thyroiditis using colour-doppler (CDUS) and contrast enhanced ultrasound (CEUS). Risk factors for central lymph node metastases (CLNM) by univariate statistics are "age < 45" (P=0.03), "tumour size >10mm" (P<0.0001), "shape wider

than tall" (P=0.0019), "CEUS hypoenhancement" (P=0.012), "CDUS peak intensity < 1" (P=0.11). Using multivariate logistic regression, the most significant risk factors for CLNM are "tumour size > 10mm" (OR 4.3, P< 0,0001) and "CEUS hypoenhancement" (OR 2.9, P =0,002).

Xue et al. from Changchun, China, include strap muscle infiltration (SMI) as risk factor, studying "Predictive Factors of Central-Compartment Lymph Node Metastasis for Clinical N0 Papillary Thyroid Carcinoma with Strap Muscle Invasion". Their single hospital study comprises the considerable number of 9,866 PTC patients recruited between 2009 and 2017, among them 281 with SMI and 50.7% with CLNM. Risk factors for CLNM in patients with SMI turn out to be "male gender" with an OR of 6.22 (P<0,02) and "age < 40" OR=9.94 (P<0,001).

LNM of PTC anatomically close to the right recurrent laryngeal nerve (RLN) represent a special challenge for the surgeon. In their paper "Metastasis of cN0 Papillary Thyroid Carcinoma of the Isthmus to the Lymph Node Posterior to the Right Recurrent laryngeal Nerve", Du et al. from Zhengzhou, China, investigate risk factors for such LNM in patients who presented clinically without central LNM. Their single hospital study comprises 357 patients who underwent bilateral central lymph node dissection. LNM posterior to the right RLN are described in 23 cases (6.7%) and only, when other LNM were prevalent (especially of the anterior right RLN with an OR of 6.9). Other significant independent factors were "tumour size > 5mm" (OR=2.8), "multifocality" (OR=2.2), and extrathyroidal extension (ETE) (OR=5.8). Zheng et al., Yantai, China focus on the "Clinical relevance and management of recurrent laryngeal nerve inlet zone lymph nodes metastasis in papillary thyroid cancer", defining the zone of 10 mm around the inlet of the RLN as "inlet zone". In their single hospital study of 947 patients with PTC, 150 received lymph node dissection, among them 47 (31%) present with such RLN inlet zone LNM. Additional ipsilateral LNM turn out to be highly predictive for RLN inlet zone LNM (OR 7.1). The authors conclude that "Once central or lateral LNM are confirmed preoperatively, RLN inlet zone dissection should be carefully performed to reduce the rate of structural recurrence in the central compartment".

A more advanced approach for lymph node staging is to combine clinical and sonographic parameters in a model with a whole set of findings. This can be done using relatively simple nomograms or better applying recent advances of artificial intelligence and machine learning. The first two among three papers on nomograms for PTC consider all stages of primaries but focus on central LNM, whereas the last one focuses on microPTC considering all possible locations of LNM.

Li et al. from Tianjin, China, describe a "Diagnostic model incorporating clinicopathological characteristics of Delphian lymph node metastasis risk profiles in papillary thyroid cancer" The Delphian lymph node is located pretracheally and considered an effective indicator of aggressive disease and recurrence. In their single hospital study with 936 PTC patients, 177 presented with LNM to the prelaryngeal nodes (18.9%). Risk factors by multivariate statistics are "male gender" (OR 4.1, P <0.0001), "younger age (OR 1.0, P =0.0039), "larger tumour size" (OR 1.1, P <0.0001), "ETE" (OR 2.2, P=0.008), "lymphovascular invasion" (OR 4.4, P=0.007), "central LNM" (OR 4.5, P< 0.0001). The proposed nomogram to predict LNM to the Delphian node is considered to be a clinically sensitive predictor of further LN in the central compartment" (ROC AUC 0.75; verified in an independent cohort).

Feng et al., Changzhou, China, present "A Nomogram Based on Clinical and Ultrasound Characteristics to Predict Central Lymph Node Metastasis of Papillary Thyroid Carcinoma". This has been developed in single hospital study with 886 PTC patients with LNM in 50% of the cases. It has to be emphasized that two different subsets of the cohort were used for training (n=617) and validation (n=269). Clinical and US variables are tested as potential predictors for central LNMs: "male sex" (OR 2.8, P<0.001), chronic lymphocytic thyroiditis (OR 1.9, P<0.001),"tumour size > 1cm" (OR 2.4, P<0.001), "tumour size > 2cm" (OR 4.0, P <0.001), "irregular margin" (OR 2.3, P <0,.001), "tumour location middle/ lower quadrant" (OR 3.6, P< 0.001). ROC analysis results in AUCs for training of 0.81 and for validation of 0.80 respectively.

The third paper on nomograms by Sun et al., Wuxi, China, "Nomogram for preoperative estimation of cervical lymph node metastasis risk in papillary thyroid microcarcinoma" focuses on micro-PTC, but not on central LNM only, as the previous papers. The single hospital study comprises 552 patients, among them 61% with LNM. Seven variables of clinical and US features are identified as potential predictors including "male sex" (OR 2.0, P =0.004), "age < 45 years" (OR 4.6, P < 0.001), "US-reported central LN status" (OR 1.9, P =0.005), "multifocality of the tumour " (OR 1.8, P =0.007), "tumour size ≥ 0.6cm" (OR 1.7, P =0.018), "ETE" (OR 3.8, P< 0.001) and "microcalcification by US" (OR 2.3, P < 0.001). In this study ROC analysis results in an AUC of 0.84.

According to a recent review, artificial intelligence and machine learning are very promising methods to improve the diagnostic sensitivity and specificity of ultrasound thyroid imaging (11). Up to now, the focus has been mainly on specification of malignancy in thyroid nodules. The following contribution of Wu et al. from Beijing, China, on "Machine learning algorithms for the prediction of central lymph node metastasis in patients with papillary thyroid cancer" takes another approach. The single hospital study in 1,103 PTC patients aims at predicting central LNM comparing seven different machine learning approaches and a set of 22 variables (including US parameters plus clinical data). For prediction of central LNM, a seven parameter machine learning gradient boosting decision tree, works best by including male sex, young age, low TPO-AB, US suspected LNM, microcalcifications, tumour size > 1.1 cm and TSH. The AUC is 0.73 in the training dataset, but no validation in a separate dataset has been performed up to now. Such approaches will gain rapidly increasing clinical relevance, provided that the data sets used are well defined, much larger and separate as well as independent sets are used for training and validation. Only cooperative networks of clinicians and computer scientists can meet these challenges.

## AUTHOR CONTRIBUTIONS

Both authors contributed equally. All authors contributed to the article and approved the submitted version.

## REFERENCES


1. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. *JAMA* (2017) 317:1338–48. doi: 10.1001/jama.2017.2719
2. Zaih M, Zhang D, Long J, Gong Y, Liu S, Li Y. The Global Burden of Thyroid Cancer and its Attributable Risk Factor in 195 Countries and Territories: A Systematic Analysis for the Global Burden of Disease Study. *Cancer Med* (2021) 10(13):4542–54. doi: 10.1002/cam4.3970
3. Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L. Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis. *New Engl J Med* (2016) 375:614–7. doi: 10.1056/NEJMp1604412
4. Preventive Services Task Force US. Screening for Thyroid Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA* (2017) 317:1882–7. doi: 10.1001/jama.2017.4011
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* (2016) 26:1–133. doi: 10.1089/thy.2015.0020
6. Sugitani I, Ito Y, Takeuchi D, Nakayama H, Masaki C, Shindo H, et al. Indications and Strategy for Active Surveillance of Adult Low-Risk Papillary Thyroid Microcarcinoma: Consensus Statements From the Japan Association of Endocrine Surgery Task Force on Management for Papillary Thyroid Microcarcinoma. *Thyroid* (2021) 31(2):183–92. doi: 10.1089/thy.2020.0330
7. Enewold L, Zhu K, Ron E, Marrogi AJ, Stojadinovic A, Peoples GE, et al. Rising Thyroid Cancer Incidence in the United States by Demographic and Tumor Characteristics, 1980-2005. *Cancer Epidemiol Biomarkers Prev* (2009) 18:784–91. doi: 10.1158/1055-9965.EPI-08-0960
8. Drozd V, Saenko V, Branovan DI, Brown K, Yamashita S, Reiners C. A Search for Causes of Rising Incidence of Differentiated Thyroid Cancer in Children and Adolescents After Chernobyl and Fukushima: Comparison of the Clinical Features and Their Relevance for Treatment and Prognosis. *Int J Environ Res Public Health* (2021) 18(7):3444. doi: 10.3390/ijerph18073444
9. Suman P, Razdan SN, Wang CE, Tulchinsky M, Ahmed L, Prinz RA, et al. Thyroid Lobectomy for T1b-T2 Papillary Thyroid Cancer With High-Risk Features. *J Am Coll Surg* (2020) 230:136–44. doi: 10.1016/j.jamcollsurg.2019.09.021
10. Gulec SA, Ahuja S, Avram AM, Bernet VJ, Bourguet P, Draganescu C, et al. A Joint Statement From the American Thyroid Association, the European Association of Nuclear Medicine, the European Thyroid Association, the Society of Nuclear Medicine and Molecular Imaging on Current Diagnostic and Theranostic Approaches in the Management of Thyroid Cancer. *Thyroid* (2021) 31(7):1009–19. doi: 10.1089/thy.2020.0826
11. Li LR, Du B, Liu HQ, Chen H. Artificial Intelligence for Personalized Medicine in Thyroid Cancer: Current Status and Future Perspectives. *Front Oncol* (2021) 10:60405. doi: 10.3389/fonc.2020.60405


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 06 August 2020
doi: 10.3389/fendo.2020.00510

# Identification of a Prognostic 3-Gene Risk Prediction Model for Thyroid Cancer

*Haiping Zhao, Shiwei Zhang, Shijie Shao and Haixing Fang**

*Department of General Surgery, The First People's Hospital of Fuyang, Hangzhou, China*

**Objective:** We aimed to screen the genes associated with thyroid cancer (THCA) prognosis, and construct a poly-gene risk prediction model for prognosis prediction and improvement.

**Methods:** The HTSeq-Counts data of THCA were accessed from TCGA database, including 505 cancer samples and 57 normal tissue samples. "edgeR" package was utilized to perform differential analysis, and weighted gene co-expression network analysis (WGCNA) was applied to screen the differential co-expression genes associated with THCA tissue types. Univariant Cox regression analysis was further used for the selection of survival-related genes. Then, LASSO regression model was constructed to analyze the genes, and an optimal prognostic model was developed as well as evaluated by Kaplan-Meier and ROC curves.

**Results:** Three thousand two hundred seven differentially expressed genes (DEGs) were obtained by differential analysis and 23 co-expression genes ($|COR| > 0.5$, $P < 0.05$) were gained after WGCNA analysis. In addition, eight genes significantly related to THCA survival were screened by univariant Cox regression analysis, and an optimal prognostic 3-gene risk prediction model was constructed after genes were analyzed by the LASSO regression model. Based on this model, patients were grouped into the high-risk group and low-risk group. Kaplan-Meier curve showed that patients in the low-risk group had much better survival than those in the high-risk group. Moreover, great accuracy of the 3-gene model was revealed by ROC curve and the remarkable correlation between the model and patients' prognosis was verified using the multivariant Cox regression analysis.

**Conclusion:** The prognostic 3-gene model composed by *GHR*, *GPR125,* and *ATP2C2* three genes can be used as an independent prognostic factor and has better prediction for the survival of THCA patients.

**Keywords: THCA, WGCNA, prognostic 3-gene risk prediction model, prediction, prognosis**

OPEN ACCESS

***Edited by:***
*Christoph Reiners, University Hospital Würzburg, Germany*

***Reviewed by:***
*Trevor Edmund Angell, University of Southern California, United States*
*Roberto Vita, University of Messina, Italy*

****Correspondence:***
*Haixing Fang*
*haixing01231@163.com*

***Specialty section:***
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

***Received:*** *18 November 2019*
***Accepted:*** *25 June 2020*
***Published:*** *06 August 2020*

***Citation:***
*Zhao H, Zhang S, Shao S and Fang H (2020) Identification of a Prognostic 3-Gene Risk Prediction Model for Thyroid Cancer. Front. Endocrinol. 11:510. doi: 10.3389/fendo.2020.00510*

## INTRODUCTION

Thyroid cancer (THCA), derived from parafollicular cells or thyroid follicular cells, is the most common endocrine malignancy accounting for about 1% of all kinds of human cancers (1). Papillary (PTC), follicular, anaplastic and medullary thyroid carcinomas are the four subtypes of THCA (2), among which papillary and follicular carcinomas are common and have better prognosis

(3), while anaplastic carcinoma is rare to be seen with extremely poor prognosis (4). Therefore, it's very important to find effective approaches for the improvement of the overall THCA prognosis.

At present, the conventional prognostic model of THCA in clinical practice is constructed according to predictive factors like age, tumor size and lymph nodule metastasis (5). With the development of high-throughput sequencing technology, mRNA expression profiles of specific cancers are easy to obtain, which helps us better find more robust prognostic signals (6). For instance, microarray-based gene expression analysis enables us to identify the important genes during tumor progression and helps to define and diagnose prognostic characteristics (7). In this way, many THCA prognostic biomarkers have been verified. However, these markers are almost single genes and have not been widely accepted (8). Polygenic combination has been reported to possess better predictive ability for cancer prognosis than single genes (9). Therefore, recent studies have involved in the identification of the biomarkers for THCA prognosis (10). However, restricted by research methods, novel biological algorithm needs to be explored to construct more accurate diagnostic or prognosis models.

In the present study, a large number of mRNA expression profiles of THCA patients were accessed from TCGA database, and modules associated with THCA were identified by WGCNA. A 3-gene risk prediction model was constructed using Cox and LASSO regression models, which could help us better predict THCA prognosis.

# MATERIALS AND METHODS

## Data Resource

Expression profiles of THCA mRNA and corresponding clinical data were accessed from TCGA database (https://cancergenome.nih.gov/), including 506 cancer samples and 56 normal tissue samples. The study was in line with the guidelines released by TCGA (http://cancergenome.nih.gov/publications/publicationguidelines).

## Identification and Confirmation of THCA-Associated Genes

"edgeR" package (https://bioconductor.org/packages/release/bioc/html/edgeR.html) was used to perform differential analysis between cancer tissues and normal tissues. Genes met the criteria ($|\log FC| > 1$ and $P < 0.05$) were considered to have significant differences.

## Module Selection With WGCNA

The mechanism of WGCNA is the research for co-expression modules and the exploration of the correlation between the gene network and the phenotypes, which is motivated by the analyses of scale-free clustering and dynamic tree cut on expression profiles. In the present study, modules that were most related to THCA tissue types in the co-expression network constructed by WGCNA package (https://cran.r-project.org/web/packages/WGCNA/index.html) were selected, and genes meeting $P < 0.05$ and $|COR| > 0.5$ were extracted for further study.

## Construction of the Prognostic Risk Prediction Model

THCA prognosis-associated genes were screened using univariant Cox regression analysis. Then, a prognostic model was constructed using the least absolute shrinkage and selection operator (LASSO). According to this model, risk score of each sample was calculated, and patients were divided into the high-risk group and low-risk group with the median risk score as the threshold. Kaplan-Meier was used to evaluate the survival of the two groups. The ROC curve was drawn for the evaluation of the prognosis performance of the model, and the area under the curve (AUC) was calculated. Furthermore, multivariant Cox regression analysis was performed to assess the correlation between the risk score and patients' prognosis. Kaplan-Meier and ROC curves of each gene in this model were plotted to make a comparison with those curves of the model.

## Statistical Analysis

Univariant and multivariant Cox regression analyses were both performed in TCGA dataset. "glmnet" package of the R software (https://www.r-project.org/) was used for LASSO statistic algorithm. IBM SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA) was applied for statistical analysis. $P < 0.05$ was considered statistically significant.

# RESULTS

## Identification of THCA-Associated Modules

As shown in **Figure 1A**, a total of 3207 DEGs were identified ($|\log FC| > 1$, $P < 0.05$). WGCNA was used to screen THCA related modules, and appropriate adjacency matrix weight parameter β (power) was selected to ensure the scale-free distribution of the co-expression network as possible (11). In the range of $1 \leq \beta \leq 20$, log k and log P(k) were calculated for linear models' construction, respectively. β is the squared value of the coefficient R. As shown in **Figure 1B**, the soft threshold (power) is higher with the elevated $R^2$, suggesting that the network closely approaches to scale-free distribution. In the present study, $\beta = 5$ ($R^2 = 0.9$ for the first time) was selected to ensure the realization of scale-free distribution as possible and make the values on the curve approach to the minimum threshold. When $\beta = 5$, the mean connectivity of RNA in the network was 5 (**Figure 1C**), which was consistent with the small-world network in the scale-free one. Then, cluster dendrogram was constructed (**Figure 1D**) and dynamic tree cut was performed (deep split = 2). Modules obtained were merged with the minimum size of 50, and 10 modules were eventually developed.

The correlation and significance between the module characteristics and sample phenotypes were calculated. Among the 10 modules, genes in blue, brown, pink and turquoise modules were verified to be most associated with THCA prognosis (**Figure 1E**). 23 THCA tissue type-associated genes were obtained from the four modules taking the $P < 0.05$ and $|COR| > 0.5$ as the threshold (**Figure 1F**).

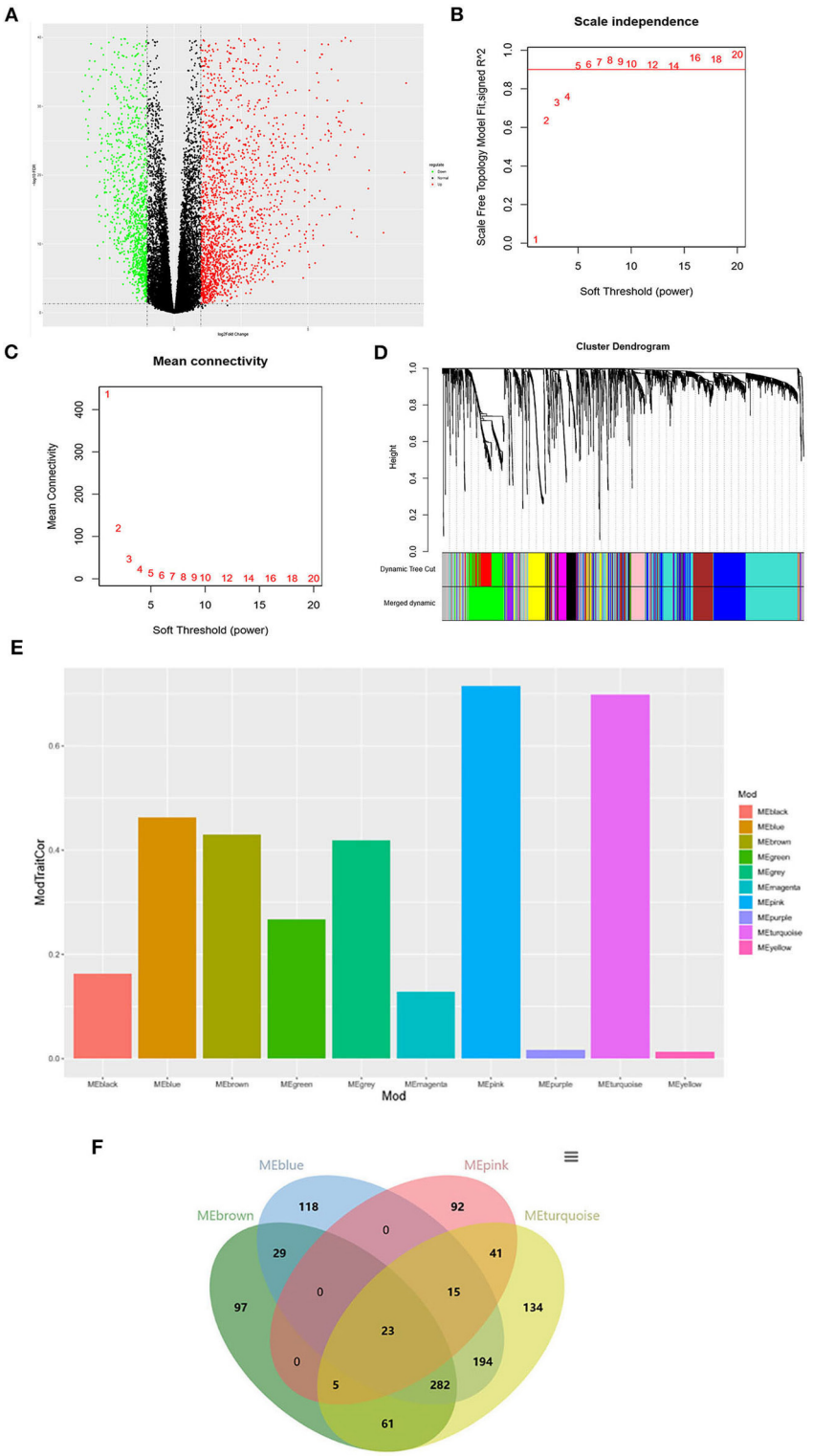


**FIGURE 1 |** Identification of the THCA tissue type-associated RNA functional modules. **(A)** Volcano plot of DEGs; **(B)** Analysis of scale-independence index for various soft threshold powers. Horizontal axis is the soft threshold (power), and vertical axis is the scale-free topology fitting indices ($R^2$). The red line refers to the standard corresponding to the $R^2$ of 0.9; **(C)** Analysis of the mean connectivity under different soft threshold powers; **(D)** Cluster dendrogram of all DEGs clustered based on a dissimilarity measure; **(E)** Distribution of average gene significance and errors in the modules associated with the progression of THCA; **(F)** Venn diagram of the genes in the four modules for co-expression genes selection.

## Construction of a Prognostic 3-Gene Risk Prediction Model for THCA

Univariant Cox regression was performed for analysis of the 23 co-expression genes, suggesting that eight genes were significantly correlated with survival as shown in **Table 1**. LASSO regression model was constructed to analyze the genes and an optimal prognostic risk prediction model was eventually developed (**Figure 2A**). Risk Score = (0.185780133850552 × GHR) + (0.277546742101366 × GPR125) + (0.257150281664915 × Atp2c2). Risk prediction was performed according to this model, and patients were ranged based on the risk scores (**Figure 2B**). The median risk score was used as the critical value to group the patients into the high-risk group ($n = 248$) and low-risk group ($n = 249$). As shown in the Kaplan-Meier curve in **Figure 2C**, patients in the high-risk group had worse overall survival (OS) than those in the low-risk group. ROC curve was plotted to predict the 3-year survival and the results showed in **Figure 2D** revealed that AUC of the 3-gene model was 0.854, which indicated the good performance of the risk score in survival prediction. Multivariant Cox proportional hazards regression analysis was then performed combined with clinical factors and the correlation between the risk score and prognosis of patients was verified (**Figure 2E**). From the heat maps of the expression profiles of these three genes (**Figure 2F**), the expression levels of *GHR*, *GPR125*, and *Atp2c2* were found to be positively correlated with the risk score, and all of them were regarded as high-risk genes.

**TABLE 1 |** Basic information of the eight prognostic genes.

| id | HR | HR.95L | HR.95H | *P*-value |
|---|---|---|---|---|
| Atp2c2 | 1.767169 | 1.266988 | 2.464812 | 0.000797 |
| GPR125 | 2.544272 | 1.465675 | 4.416615 | 0.000905 |
| GHR | 2.11237 | 1.316811 | 3.38857 | 0.001927 |
| CLMN | 1.794182 | 1.11235 | 2.893954 | 0.016554 |
| CYTH3 | 2.402596 | 1.039985 | 5.550527 | 0.040195 |
| PLA2R1 | 1.426271 | 1.008296 | 2.01751 | 0.044786 |
| RYR2 | 1.278786 | 1.003806 | 1.629094 | 0.046512 |
| C8orf88 | 1.551333 | 1.002698 | 2.400158 | 0.048602 |

## Evaluation of the 3-Gene Risk Prediction Model

Kaplan-Meier curves of the three genes were drawn using the log rank test. As shown in **Figures 3A–C**, THCA patients with low expression of *GHR*, *GPR125,* and *Atp2c2* had longer survival time, indicting that these three genes were high-risk genes, which was in agreement with the results predicted by univariant Cox regression analysis. Furthermore, ROC curves (**Figures 3D–F**)

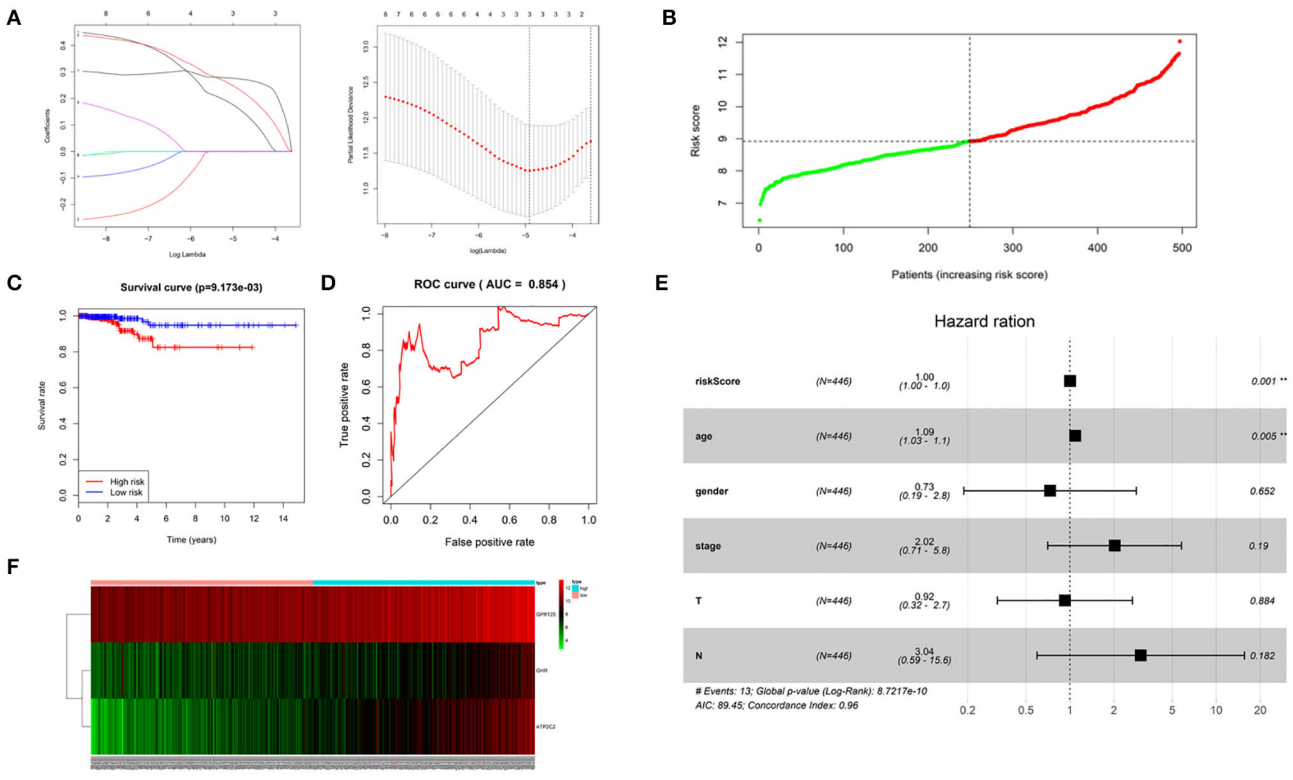


**FIGURE 2 |** Construction of a 3-gene risk prediction model. **(A)** LASSO regression model; **(B)** 3-gene based distribution of risk scores; **(C)** Survival analysis of real hub genes in the TCGA-THCA dataset; **(D)** ROC curve of real hub genes in the TCGA-THCA dataset; **(E)** The correlation between the risk score and patients' prognosis; **(F)** Heatmap of the 3 genes expression profiles.

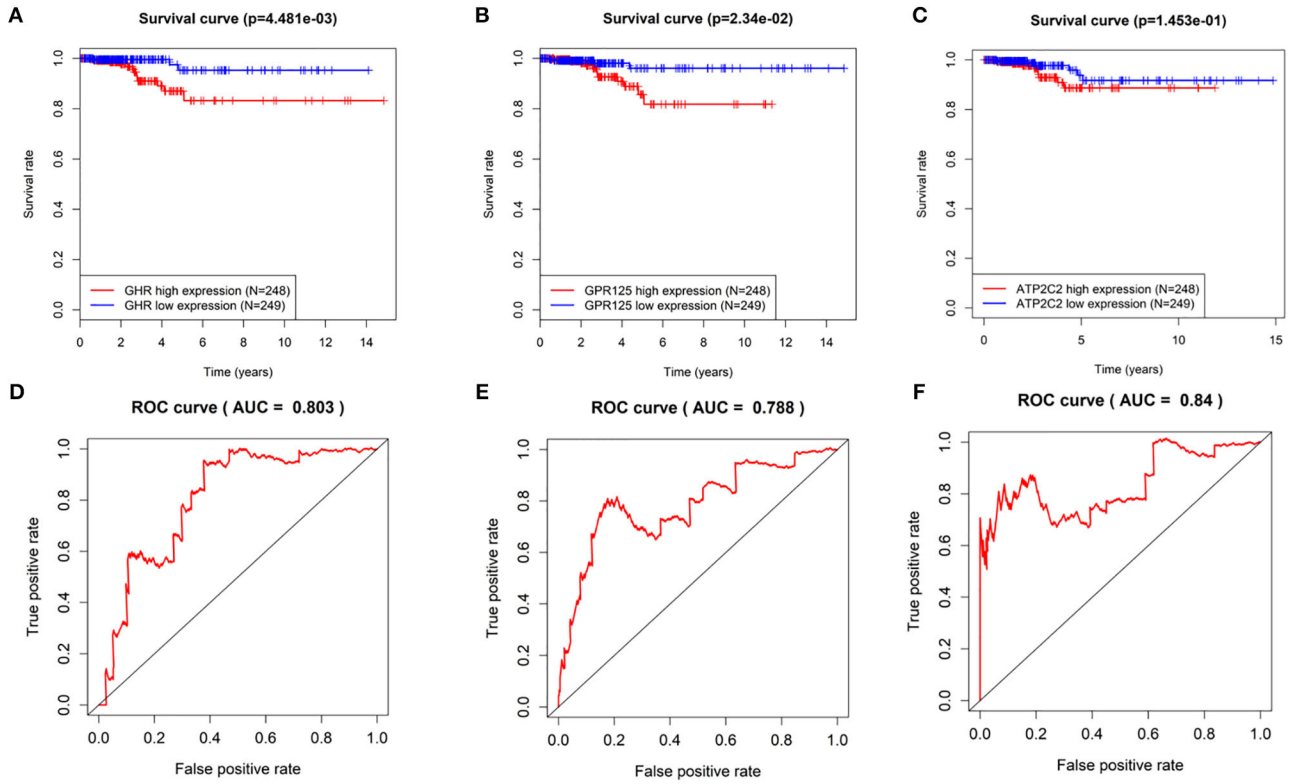


**FIGURE 3 |** The evaluation of the 3-gene risk prediction model. **(A–C)** Survival analyses of GHR, GPR125, and Atp2c2 in the TCGA-THCA dataset; **(D–F)** ROC analyses of GHR, GPR125 and Atp2c2 in the TCGA-THCA dataset.

revealed that the AUC of *GHR*, *GPR125,* and *Atp2c2* was 0.803, 0.788, and 0.84, respectively, all of which were smaller than that of the 3-gene risk prediction model. Findings above demonstrate that risk score is a good indicator for prognosis, and the 3-gene model has a higher accuracy.

## DISCUSSION

With the development of the microarray and RNA sequencing technologies, new era of large data on biology is coming. It has been reported that microarray-based gene expression analysis could achieve characterization in human cancers, identification of the important genes during tumorigenesis and the definition as well as the diagnosis of prognostic features (7). However, the role of genes as prognosis factors has been few investigated (12). In the present study, a large amount of RNA-seq profiles and clinical prognosis data of THCA patients were accessed from TCGA database, and co-expression gene modules were screened using WGCNA. Studies have shown that gene modules are much reliable in cancer prognosis than biomarkers. While there are few studies on the cross-talk among the modules, and some important modules might be ignored (13). Therefore, in our study, gene co-expression network was constructed via WGCNA, and was used to identify THCA tissue type-associated gene modules, including blue, brown, pink and turquoise. Twenty-three common genes were obtained from the four modules, and an optimal prognostic 3-gene risk prediction model was then constructed by univariant Cox and LASSO regression analyses. Along with the LASSO model, all independent variables can be processed simultaneously, verifying the more accurate performance than the stepwise regression model (14). *GHR*, *GPR125,* and *Atp2C2* were the three genes in this model. *GHR* is a kind of protein-coding gene coding transmembrane receptors of the growth hormone. In prior studies, *GHR* has been verified to be a oncogene in some cancers, such as breast cancer (15), pancreatic ductal carcinoma (16) and melanoma (17), but the role in THCA prognosis is firstly reported. *GPR125*, a 57-KDa factor for transmembrane signal transduction, is considered to play a key role in cell adhesion and signal transduction (18). It's reported that *GPR125* is up-regulated in human cerebral cancer tissues (19) and promotes cell adhesion as well as the formation of myelosarcoma (20). In our study, *GHR* and *GPR125* were verified as high-risk genes in THCA, which was consistent with the previous studies. Moreover, we found that these two genes could be used as independent risk predictive factors, but the accuracy was lower than that of the 3-gene risk prediction model, which was further verified by ROC and Kaplan-Meier curves.

As the expression profiles of THCA and clinical information are just from one dataset of TCGA, the samples for analyzing the prognostic 3-gene model are limited. In addition, the model constructed in this study might be not available when it comes to other databases, and it's necessary to improve the model with

more datasets. In a word, a 3-gene model is constructed to be an independent predictor in this study, which provides novel view and approach for the prognosis of THCA patients.

## DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

## AUTHOR CONTRIBUTIONS

HZ contributed to the study design and gave the final approval of the version to be submitted. SZ conducted the literature search and performed data analysis and drafted. SS acquired the data and revised the article. HF wrote the article. All authors contributed to the article and approved the submitted version.

## REFERENCES


1. Hedayati M, Zarif Yeganeh M, Sheikholeslami S, Afsari F. Diversity of mutations in the RET proto-oncogene and its oncogenic mechanism in medullary thyroid cancer. *Crit Rev Clin Lab Sci*. (2016) 53:217–27. doi: 10.3109/10408363.2015.1129529
2. Carling T, Udelsman R. Thyroid cancer. *Annu Rev Med*. (2014) 65:125–37. doi: 10.1146/annurev-med-061512-105739
3. Dralle H, Machens A, Basa J, Fatourechi V, Franceschi S, Hay ID, et al. Follicular cell-derived thyroid cancer. *Nat Rev Dis Primers*. (2015) 1:15077. doi: 10.1038/nrdp.2015.77
4. Smallridge RC, Copland JA. Anaplastic thyroid carcinoma: pathogenesis and emerging therapies. *Clin Oncol*. (2010) 22:486–97. doi: 10.1016/j.clon.2010.03.013
5. Shaha AR. Implications of prognostic factors and risk groups in the management of differentiated thyroid cancer. *Laryngoscope*. (2004) 114:393–402. doi: 10.1097/00005537-200403000-00001
6. Zhao QJ, Zhang J, Xu L, Liu FF. Identification of a five-long non-coding RNA signature to improve the prognosis prediction for patients with hepatocellular carcinoma. *World J Gastroenterol*. (2018) 24:3426–39. doi: 10.3748/wjg.v24.i30.3426
7. Hebrant A, Dom G, Dewaele M, Andry G, Trésallet C, Leteurtre E, et al. mRNA expression in papillary and anaplastic thyroid carcinoma: molecular anatomy of a killing switch. *PLoS ONE*. (2012) 7:e37807. doi: 10.1371/journal.pone.0037807
8. Brennan K, Holsinger C, Dosiou C, Sunwoo JB, Akatsu H, Haile R, et al. Development of prognostic signatures for intermediate-risk papillary thyroid cancer. *BMC Cancer*. (2016) 16:736. doi: 10.1186/s12885-016-2771-6
9. Zuo S, Dai G, Ren X. Identification of a 6-gene signature predicting prognosis for colorectal cancer. *Cancer Cell Int*. (2019) 19:6. doi: 10.1186/s12935-018-0724-7
10. Li X, Dai D, Wang H, Wu B, Wang R. Identification of prognostic signatures associated with long-term overall survival of thyroid cancer patients based on a competing endogenous RNA network. *Genomics*. (2019) 112:1197–207. doi: 10.1016/j.ygeno.2019.07.005
11. Li J, Yu X, Liu Q, Ou S, Li K, Kong Y, et al. Screening of important lncRNAs associated with the prognosis of lung adenocarcinoma, based on integrated bioinformatics analysis. *Mol Med Rep*. (2019) 19:4067–80. doi: 10.3892/mmr.2019.10061
12. Tavares C, Melo M, Cameselle-Teijeiro JM, Soares P, Sobrinho-Simoes M. Endocrine tumours: genetic predictors of thyroid cancer outcome. *Eur J Endocrinol*. (2016) 174:R117–26. doi: 10.1530/EJE-15-0605
13. Cui ZJ, Zhou XH, Zhang HY. DNA methylation module network-based prognosis and molecular typing of cancer. *Genes*. (2019) 10:571. doi: 10.3390/genes10080571
14. Gu JX, Zhang X, Miao RC, Xiang XH, Fu YN, Zhang JY, et al. Six-long non-coding RNA signature predicts recurrence-free survival in hepatocellular carcinoma. *World J Gastroenterol*. (2019) 25:220–32. doi: 10.3748/wjg.v25.i2.220
15. Arumugam A, Subramani R, Nandy SB, Terreros D, Dwivedi AK, Saltzstein E, et al. Silencing growth hormone receptor inhibits estrogen receptor negative breast cancer through ATP-binding cassette sub-family G member 2. *Exp Mol Med*. (2019) 51:2. doi: 10.1038/s12276-018-0197-8
16. Subramani R, Lopez-Valdez R, Salcido A, Boopalan T, Arumugam A, Nandy S, et al. Growth hormone receptor inhibition decreases the growth and metastasis of pancreatic ductal adenocarcinoma. *Exp Mol Med*. (2014) 46:e117. doi: 10.1038/emm.2014.61
17. Proudfoot NJ, Gil A, Whitelaw E. Studies on messenger RNA 3' end formation in globin genes: a transcriptional interference model for globin gene switching. *Prog Clin Biol Res*. (1985) 191:49–65.
18. Wu Y, Chen W, Gong L, Ke C, Wang H, Cai Y. Elevated G-protein receptor 125. (GPR125) expression predicts good outcomes in colorectal cancer and inhibits Wnt/beta-catenin signaling pathway. *Med Sci Monit*. (2018) 24:6608–16. doi: 10.12659/MSM.910105
19. Pickering C, Hägglund M, Szmydynger-Chodobska J, Marques F, Palha JA, Waller L, et al. The adhesion GPCR GPR125 is specifically expressed in the choroid plexus and is upregulated following brain injury. *BMC Neurosci*. (2008) 9:97. doi: 10.1186/1471-2202-9-97
20. Fu JF, Yen TH, Chen Y, Huang YJ, Hsu CL, Liang DC, et al. Involvement of Gpr125 in the myeloid sarcoma formation induced by cooperating MLL/AF10(OM-LZ) and oncogenic KRAS in a mouse bone marrow transplantation model. *Int J Cancer*. (2013) 133:1792–802. doi: 10.1002/ijc.28195


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 25 August 2020
doi: 10.3389/fendo.2020.00551

# Predictive Factors of Lymph Node Metastasis in Patients With Papillary Microcarcinoma of the Thyroid: Retrospective Analysis on 293 Cases

*Fabio Medas[1]*, Gian Luigi Canu[1], Federico Cappellacci[1], Francesco Boi[2], Maria Letizia Lai[3], Enrico Erdas[1] and Pietro Giorgio Calò[1]*

*[1] Department of Surgical Sciences, University of Cagliari, Cagliari, Italy, [2] Endocrinology, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy, [3] Division of Anatomy and Pathological Histology, University of Cagliari, Cagliari, Italy*

OPEN ACCESS

***Edited by:***
*Christoph Reiners, University Hospital Würzburg, Germany*

***Reviewed by:***
*Yevgeniya Kushchayeva, University of South Florida, United States*
*Valentina Drozd, The International Fund "Help for Patients With Radiation-Induced Thyroid Cancer 'ARNICA'", Minsk, Belarus*

****Correspondence:***
*Fabio Medas*
*fabiomedas@unica.it*

***Specialty section:***
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

***Received:*** *18 February 2020*
***Accepted:*** *06 July 2020*
***Published:*** *25 August 2020*

***Citation:***
*Medas F, Canu GL, Cappellacci F, Boi F, Lai ML, Erdas E and Calò PG (2020) Predictive Factors of Lymph Node Metastasis in Patients With Papillary Microcarcinoma of the Thyroid: Retrospective Analysis on 293 Cases. Front. Endocrinol. 11:551. doi: 10.3389/fendo.2020.00551*

**Introduction:** Papillary thyroid microcarcinoma (PTMC) is defined as a tumor with a larger diameter ≤1 cm and is considered having an indolent course and an excellent prognosis. Nevertheless, the incidence of lymph node metastasis in PTMC is not negligible, reaching up to 65% in some series. The aim of this study was to assess the incidence of lymph node metastasis in patients with PTMC and to evaluate predictive factors for lymph node metastasis.

**Methods:** We included in this retrospective observational study patients who underwent thyroidectomy with pathological diagnosis of PTMC at our department from January 2003 to June 2019.

**Results:** Two hundred ninety-three patients were included in the study. The incidence of lymph node metastasis was 13.7%. Multivariate analysis revealed as independent risk factors for lymph node metastasis age <45 years, nodule size ≥6 mm, tall cell variant of PTC, extrathyroidal extension, and angioinvasion. Conversely, autoimmune thyroiditis was found as a protective factor for lymph node metastasis. A subgroup of patients, with nodule size ≤5 mm, presented non-aggressive features.

**Conclusion:** The incidence of lymph node metastasis in PTMC is considerable; the size of the tumor appears to be the most significant predictive factor for lymph node metastasis. The traditional cut-off value used for definition of microcarcinoma could be reconsidered to identify patients with an indolent course of the tumor, where active surveillance could be the appropriate treatment, and on the other hand, patients with potentially aggressive tumors requiring an adequate surgical intervention.

**Clinical Trial Registration:** The trial was registered at ClinicalTrials.gov (ID: NCT04274829).

**Keywords: thyroid carcinoma, lymph node metastasis, microcarcinoma, thyroidectomy, lymph node dissection**

## INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common variety of differentiated thyroid carcinoma. Its incidence has increased in the last decades, mainly due to the diffusion of ultrasound (US) examination of the neck (1–3). Furthermore, the diffusion of screening programs for thyroid cancer has allowed detecting a larger number of tumors at an early stage. Papillary thyroid microcarcinoma (PTMC) is defined as a tumor with the larger diameter ≤1 cm (4, 5). In the absence of aggressive features, the American Thyroid Association (ATA) guidelines include this entity in the low-risk category, with a risk of recurrence estimated as 1–2% (6); on the other side, if aggressive characteristics are present, the risk of relapse is not negligible, with lymph node (LN) metastases and extrathyroidal extension being the most important predictive factors of recurrence. Because of its indolent course and its excellent prognosis, in the last few years, active surveillance has been purposed as an alternative to immediate surgery (7). Nevertheless, the incidence of lymph node metastasis in PTMC is not negligible, also in patients with clinically uninvolved lymph nodes (cN0), reaching approximately up to 65% in some series (8–11); this finding raises questions on the most appropriate treatment for PTMC.

The aim of this study was to assess the incidence of lymph node metastasis in patients with PTMC and to evaluate predictive factors for lymph node metastasis.

## METHODS

We included in this retrospective observational study patients who underwent thyroidectomy at our department from January 2003 to June 2019 with pathological diagnosis of PTMC, defined as a PTC with a larger diameter equal or inferior to 1 cm. Patients were selected from a prospectively institutional maintained database including all patients with thyroid carcinoma. Exclusion criteria were concomitant tumors with a larger diameter >1 cm, patients in which an evaluation of lymph node status was not available because any sample of lymph node was obtained during surgery, and those with incomplete data.

The primary outcome of the study was the incidence of lymph node metastasis in PTMC, and the secondary was to identify independent risk factors for lymph node metastasis.

Preoperative assessment included anamnesis, physical examination, blood tests to assess thyroid function and autoimmune thyroiditis, and high-resolution US of the neck with careful evaluation of the central and of the lateral compartment of the neck. Fine needle cytology aspiration (FNAC) was performed in case of suspicious nodules; the cut-off value for FNAC was 5 mm. An FNAC with dosage of Thyroglobulin (Tg) was performed in case of positive lymph nodes at US in central or lateral neck compartment. Thyroid scintigraphy was done only in case of hyperthyroidism, defined as low serum TSH (<0.4 mIU/L) and normal or high serum FT3 and FT4. Preoperative laryngoscopy was routinely performed to assess vocal fold mobility.

Surgical procedure consisted of extracapsular total thyroidectomy (TT) or lobo-isthmectomy (LH). In case of low-risk tumors with clinically uninvolved lymph nodes (cN0), a lymph node sampling of the central compartment was performed. Prophylactic central lymph node dissection (CLND) was done in case of clinically uninvolved central lymph neck nodes (cN0) in high-risk tumors, including patients with preoperative US or intraoperative suspicion of extracapsular extension of the tumor, or in case of clinically involved lateral neck nodes (cN1b), as suggested from ATA guidelines. A therapeutic CLND was performed in case of preoperative or intraoperative suspicion of lymph node metastasis of the central compartment. Therapeutic lateral neck dissection (LND) was performed only in case of preoperative evidence of lateral neck node metastasis.

In case of multifocal tumor, the tumor size was determined as the larger diameter of primary tumor. Extrathyroidal extension was defined as the presence of gross infiltration of perithyroidal tissues found at pathological examination, and vascular invasion as the invasion of vessels in the tumor capsule or beyond, with intravascular tumor cells attached to the vessel wall.

Autoimmune thyroiditis was defined in case of positive Thyroglobulin-Antibodies (Tg-Ab) and/or Thyroid Peroxidase-Antibodies (TPO-Ab) and confirmed at pathological examination.

Tall cell variant of PTC was defined in case of presence of columnar cells (height is twice the width) representing at least 50% of tumor cells.

Lymph node yield was defined as the number of lymph nodes retrieved after lymphectomy, and lymph node ratio as the ratio of metastatic lymph nodes out of the total lymph nodes removed.

Four preoperative and seven pathologic features were tested as risk factors for lymph node metastasis: sex, age, hyperthyroidism, autoimmune thyroiditis, size of the tumor, thyroid weight, histological subtype of PTC, multicentricity, angioinvasion, and the presence of extrathyroidal extension.

Univariate analysis was conducted using chi-squared test for categorical variables and Student's *t*-test for continuous variables. Factors with a *p*-value ≤0.10 in univariate analysis were considered potentially significant and were included in the multivariate analysis. Logistic regression was employed to identify independent risk factors for lymph node metastasis; results were considered statistically significant for *p*-value <0.05.

Calculations were performed with MedCalc® vers. 19.1.3. Continuous variables are reported as the mean ± standard deviation of the mean.

## RESULTS

During the study period, a total number of 584 patients with pathological diagnosis of PTMC underwent surgical therapy; 240 patients were excluded because pathologic N status was not assessed, and 51 because of incomplete data. Therefore, 293 patients met inclusion criteria and were included in the study.

Preoperative data are reported in **Table 1**. Diagnosis of PTMC was incidental in 115 (39.2%) patients, whereas it was suspected at preoperative exams in 178 (60.8%) cases. There were 61

**TABLE 1 |** Preoperative data and surgical procedure.

| | Patients ($n = 293$) |
|---|---|
| **Sex** | |
| Male | 61 (20.8%) |
| Female | 232 (79.2%) |
| Age, years (range) | 49.8 ± 14.3 (15–80) |
| Hyperthyroidism | 44 (15%) |
| Autoimmune thyroiditis | 175 (59.7%) |
| Preoperative diagnosis of PTMC | 178 (60.8%) |
| - Hypoechoic nodule | 121 (67.9%)* |
| - Microcalcifications | 21 (11.8%)* |
| - Intranodular vascularization | 84 (47.2%)* |
| Preoperative diagnosis of metastatic lymph nodes at US | 11 (3.8%) |
| **Surgical procedure** | |
| - LH + LNS | 9 (3.1%) |
| - LH + CLND | 2 (0.7%) |
| - TT + LNS | 175 (59.7%) |
| - TT + CLND | 100 (34.1%) |
| - TT + CLND + LND | 7 (2.4%) |

*US, ultrasound; TT, total thyroidectomy; LH, lobo-isthmectomy; LNS, lymph node sampling; CLND, central compartment lymph node dissection; LND, lateral neck dissection.*
**Calculated on 178 patients with preoperative diagnosis of PTMC.*

**TABLE 2 |** Pathological features of 293 patients with papillary thyroid carcinoma.

| | Patients ($n = 293$) |
|---|---|
| Nodule size, mm (range) | 5.8 ± 2.9 (0.5–10) |
| Thyroid weight, g (range) | 32.1 ± 26.7 (8–164) |
| **Histotype** | |
| PTC | 182 (62.1%) |
| FV-PTC | 63 (21.5%) |
| Tall cell carcinoma | 48 (16.4%) |
| Extrathyroidal extension | 23 (7.8%) |
| Multicentric carcinoma | 97 (33.1%) |
| Angioinvasive carcinoma | 19 (6.5%) |
| Lymph node yield (range) | 4.3 ± 4.8 (1–33) |
| Lymph node size, mm (range) | 0.7 ± 0.4 (0.4–21) |
| Lymph node metastasis | 40 (13.7%) |
| Unexpected lymph node metastasis* | 29 (9.8%) |
| Number of involved LN per patient** (range) | 2.5 ± 2.4 (1–12) |
| Lymph node ratio** (range) | 0.49 ± 0.32 (0.06–1) |
| Extranodal extension | 4 (1.4%) |

*PTC, papillary thyroid carcinoma; FV-PTC, follicular variant of PTC.*
**Pathological diagnosis of lymph node metastasis that was unsuspected at preoperative US examination.*
***Calculated on 40 patients with lymph node metastasis.*

(20.8%) males and 232 (79.2%) females, with a mean age of 49.8 ± 14.3 years. Autoimmune thyroiditis was present in 175 (59.7%) cases, and 44 (15%) patients had a hyperthyroidism status (21 had a Graves' disease, 21 a toxic multinodular goiter, and 3 a toxic adenoma).

Among the 178 patients with a preoperative suspicion of PTMC, US examination demonstrated a hypoechogenic nodule in 121 (67.9%) cases, microcalcifications in 21 (11.8%) patients, and intranodular vascularization in 84 (47.2%) cases.

A lobo-isthmectomy associated with lymph node sampling of the central compartment was performed in 9 (3.1%) cases and with complete CLND in 2 (0.7%) patients. Total thyroidectomy with lymph node sampling was performed in 175 (59.7%) cases, associated with prophylactic or therapeutic CLND in 100 (34.1%) patients and to LND in 7 (2.4%) cases.

Full pathological features are reported in **Table 2**. Overall, the lymph node yield was 4.3 ± 4.8; specifically, the lymph node yield was 2.1 ± 1.1 in lymph node sampling, 7.3 ± 4.7 in CLND, and 24.8 ± 8.16 in LND.

The incidence of lymph node metastasis was 13.7%, with a lymph node ratio of 0.49 ± 0.32. Specifically, the incidence of metastasis of the central compartment was 12.9%, and that of the lateral neck compartment was 2%. Unexpected lymph node metastasis was found in 29 (9.8%) patients, whereas in 11 (3.8%) patients, pathological examination confirmed preoperative US finding. Extranodal extension was found in 4 (1.4%) patients.

During univariate analysis, age, autoimmune thyroiditis, nodule size, tumor histotype, extrathyroidal extension, and angioinvasion were found as potentially significant risk factors for lymph node metastasis (**Table 3**).

Multivariate analysis revealed age <45 years (36.4% in pN0 group vs. 57.5% in pN1 group; OR 3.249; $p = 0.0041$), nodule size ≥ 6 mm (47% in pN0 group vs. 77.5% in pN1 group; OR 3.878; $p = 0.0476$), tall cell variant of PTC (13% in pN0 group vs. 37.5% in pN1 group; OR 3.479; $p = 0.0074$), extrathyroidal extension (5.5% in pN0 group vs. 22.5% in pN1 group; OR 3.642; $p = 0.0196$), and angioinvasive carcinoma (4% in pN0 group vs. 22.5% in pN1 group; OR 3.49; $p = 0.0322$) as independent risk factors for lymph node metastasis. Conversely, autoimmune thyroiditis was found as a protective factor for LN metastasis (63.2% in pN0 group vs. 37.5% in pN1 group; OR 0.348; $p = 0.0408$).

As reported in **Figure 1**, a further analysis demonstrated a positive correlation between the tumor size and the lymph node ratio, with a correlation coefficient of 0.2409 (CI 0.1134–0.3606; $p = 0.0003$).

## DISCUSSION

Papillary thyroid microcarcinoma is considered a tumor with an indolent behavior and a low risk of recurrence; for these reasons, ATA 2015 guidelines included this entity in the low-risk category, not recommending post-operative RAI, and also suggesting active surveillance management as an alternative to surgery in patients without evidence of lymph node metastasis or local invasion.

Nevertheless, in a subset of patients, PTMC exhibits aggressive behavior, presenting with lymph node metastasis and, in some cases, with local recurrence. The incidence of node metastasis

**TABLE 3 |** Univariate and multivariate analyses of preoperative data and pathological features of 293 patients with papillary thyroid microcarcinoma.

| | Univariate analysis | | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|
| | **pN0 (*n* = 253)** | **pN1 (*n* = 40)** | ***p*-value** | **Regression coefficient** | **Odds ratio** | **95% CI** | ***p*-value** |
| Male sex | 51 (20.2%) | 10 (25%) | 0.6232 | | | | |
| Age <45 | 92 (36.4%) | 23 (57.5%) | 0.0178 | 1.17840 | 3.2492 | 1.4531–7.2655 | **0.0041** |
| Hyperthyroidism | 38 (15%) | 6 (15%) | 0.8142 | | | | |
| Autoimmune thyroiditis | 160 (63.2%) | 15 (37.5%) | 0.0036 | 0.84531 | 0.3488 | 0.1751–0.6948 | **0.0408** |
| Nodule size ≥6 mm | 119 (47%) | 31 (77.5%) | 0.0006 | −0.93025 | 3.8786 | 1.7742–8.4791 | **0.0476** |
| Thyroid weight | 31.4 ± 32.4 | 36.7 ± 25.7 | 0.2381 | | | | |
| Histotype | | | 0.0005 | | | | |
| PTC | 164 (64.8%) | 18 (45%) | | 1.000 | 1.000 | Reference | |
| FV-PTC | 56 (22.1%) | 7 (17.5%) | | 0.26498 | 1.3034 | 0.4762–3.5678 | 0.6060 |
| Tall cell carcinoma | 33 (13%) | 15 (37.5%) | | 1.24695 | 3.4797 | 1.3980–8.6610 | **0.0074** |
| Extrathyroidal extension | 14 (5.5%) | 9 (22.5%) | 0.0006 | 1.29253 | 3.6420 | 1.2302–10.7826 | **0.0196** |
| Multicentric carcinoma | 80 (31.6%) | 17 (42.5%) | 0.2388 | | | | |
| Angioinvasive carcinoma | 10 (4%) | 9 (22.5%) | <0.0001 | 1.25005 | 3.4905 | 1.1117–10.9595 | **0.0322** |

*PTC, papillary thyroid carcinoma; FV-PTC, follicular variant of PTC. Bold values indicates statistically significant.*

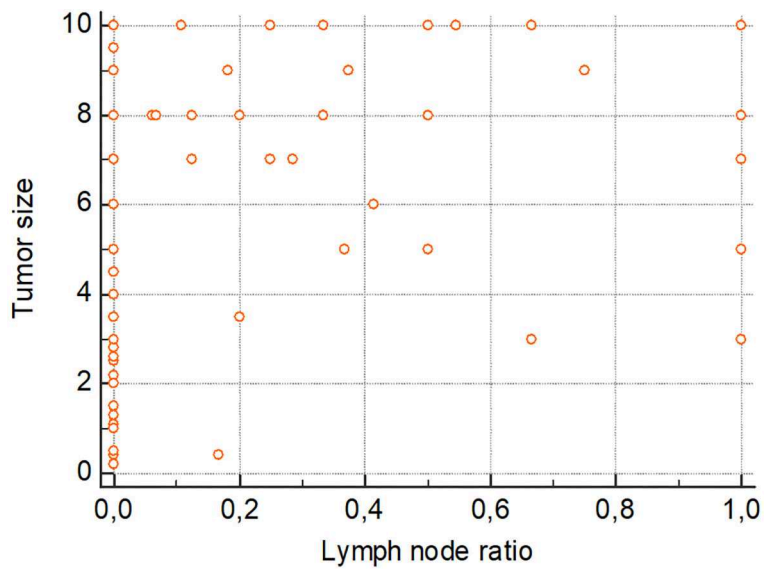


**FIGURE 1 |** Scatter diagram reporting correlation between tumor size and lymph node ratio. Correlation coefficient = 0.2409; CI = 0.1134–0.3606; *p*-value = 0.0003.

in PTMC varies widely in the literature, ranging from 29.5 to 65% (8–10, 12–15), and node metastasis is considered the main predictive factor for local recurrence (16, 17).

The aim of this study was to assess potential risk factors for lymph node metastasis to identify patients with PTMC in whom aggressive surgery could be justified.

In the present study, ∼13% of patients had lymph node metastasis of the central compartment, and 2% of the lateral neck compartment. Interestingly, we observed three cases of "skip metastasis" in which only the lateral compartment was involved, without evidence of node metastasis in the central compartment.

According to other studies present in the literature (12, 13, 18–23), we found younger age, tumor size, tall cell variant of PTC, extrathyroidal extension, and angioinvasion as independent risk factors for lymph node metastases.

It is interesting to note that size of the tumor appears to be an independent predictive factor for lymph node metastasis in almost all the series reported in the literature. Specifically, in our study we found an incidence of lymph node metastasis of 6.3% in patients with tumors with size up to 5 mm, and of 20.6% in patients with larger tumors; we also reported a significant correlation between tumor size and lymph node ratio.

**TABLE 4 |** Characteristic of tumors considering a cut-off value of 6 mm.

| | Tumors <6 mm ($n = 143$) | Tumors ≥6 mm ($n = 150$) | $p$ |
|---|---|---|---|
| Nodule size (mm) | 3.1 ± 1.5 | 8.3 ± 1.5 | $p < 0.001$ |
| Histotype | | | $p < 0.001$ |
| PTC | 105 (73.4%) | 77 (51.3%) | |
| FV-PTC | 28 (19.6%) | 35 (23.3%) | |
| Tall cell carcinoma | 10 (7%) | 38 (25.3%) | |
| Extrathyroidal extension | 5 (3.5%) | 18 (12%) | 0.0128 |
| Multicentric carcinoma | 32 (22.4%) | 65 (43.3%) | $p < 0.001$ |
| Angioinvasive carcinoma | 2 (1.4%) | 17 (11.3%) | 0.001 |
| Lymph node yield | 3.4 ± 3.5 | 5.2 ± 5.6 | 0.001 |
| Lymph node metastasis | 9 (6.3%) | 31 (20.7%) | $p < 0.001$ |
| Number of involved LN per patient* | 1.9 ± 2 | 2.7 ± 2.6 | 0.41 |
| Lymph node ratio* | 0.5 ± 0.3 | 0.5 ± 0.3 | 0.85 |

**Calculated on 9 and 31 patients with metastatic lymph nodes in the first and second group, respectively.*

Wang et al. (24) reported that 5.75 mm at preoperative ultrasound is the best cut-off value to predict the risk of central lymph node metastasis. In the study of Gong et al. (25), including over 1,100 patients, a cut-off value of 8.5 mm was calculated based on receiver operating characteristics (ROC) curves: tumors with larger size demonstrated an aggressive behavior with a poorer prognosis, including, other than a higher incidence of lymph node metastasis, the presence of extrathyroidal extension, multifocality, and local recurrence. Xu et al. (23) reported in a large series of over 3,000 patients with PTMC that a tumor size larger than 7 mm is strongly associated with a higher incidence of lymph node metastasis, suggesting in these patients a careful preoperative examination of central and lateral compartment and an aggressive surgical approach.

Furthermore, in our series, ∼10% of patients with cN0 stage had lymph node metastasis at final pathology; when considering only patients with tumors larger than 6 mm, the incidence of unexpected lymph node metastasis was nearly 18%.

As extensively reported in **Table 4**, in our series, the subgroup of patients with tumors with size up to 5 mm presented significantly with non-aggressive features: as already remarked, the incidence of lymph node metastasis was 6.3% in this group, whereas it was 20.7% in tumors larger than 5 mm. Furthermore, angioinvasion was present only in 2 (1.4%) cases and extrathyroidal extension only in 5 (3.5%) patients in the first group, while it was found in 17 (11.3%) and 18 (12%) cases in the larger group, respectively.

It is important to note that, among all the predictive factors of lymph node metastasis, the only feature preoperatively assessable is the size of the tumor; conversely, the other features, including extrathyroidal extension, tall cell variant of PTC, and angioinvasion, are pathological findings that are significant in follow-up but are not helpful for surgeons at the operating table.

Given all these considerations, it is reasonable to assume that the cut-off value of 10 mm, traditionally used as a discriminant for the definition of microcarcinoma, is too high to discriminate tumors with favorable pathological features from those with potential aggressive behavior that could require a more aggressive surgical approach.

As already stated, an active surveillance has been purposed for PTMC as an alternative to surgery (7). However, recent evidences deriving from the works of Choi et al. (26) and Oh et al. (27) suggested that the indication for active surveillance should be carefully weighted and applied for selected patients. In fact, the authors reported that some low-risk PTMC can progress significantly during the delayed intervention period for active surveillance, and that patients who underwent delayed surgical intervention had more aggressive disease and unfavorable oncologic outcome than those who underwent immediate surgery.

In our series, the diagnosis of PTMC was incidental in about 40% of the patients; in this case, even if the incidence of lymph node metastasis and of other pathologic aggressive features is uncommon, a risk stratification following ATA guidelines is recommended to identify potential tumors with medium or high risk of recurrence.

On the contrary, diagnosis of PTMC was made preoperatively in nearly 60% of the patients. In this case, an accurate preoperative US evaluation of cervical lymph nodes should always be performed, especially in tumors with size larger than 6 mm. Furthermore, intraoperative exploration of the VI level should be accurate, considering that US has low accuracy for node metastasis of the central compartment; a recent meta-analysis of Zhao et al., which included 19 articles and over 4,000 patients with PTC, reported a poor sensitivity of US in detecting metastases of the central compartment (pooled sensitivity of 33%, range 10–57%) with an incidence of lymph node metastases of 48% (28). Xue et al. reported similar results, with a sensitivity of US for diagnosis of metastatic lymph nodes of the central compartment of 22–55% (29).

A therapeutic neck dissection is always indicated in case of clinically involved lymph nodes. On the other hand, in case of clinically uninvolved lymph nodes, a prophylactic lymph node dissection of the central compartment is not indicated, also considering ATA guidelines.

Furthermore, it should be underlined that the incidence of lymph node metastasis depends from the tumor histotype. In our series, we found the tall cell carcinoma as an independent risk factor for lymph node metastasis: more than one third of patients with metastatic lymph nodes had a tall cell carcinoma. On the other hand, a follicular variant of PTC seems to be a less aggressive variant, with a lower incidence of lymph node metastasis, even if this difference was not significant in our series.

Another interesting finding is that we identified autoimmune thyroiditis as a protective factor for lymph node metastasis. In our series, the incidence of lymph node metastasis was 8.5% in patients with autoimmune thyroiditis and 21% in patients without autoimmune thyroiditis. This finding is discordant with other studies that identified autoimmune thyroiditis being associated with the aggressive behavior of PTC (30–32), including a higher incidence of lymph node metastasis. Indeed, some studies indicated that a different antibody status is associated

with a distinct risk of development of PTC and of its prognosis: Paparodis demonstrated that high levels of TPOAb protect against DTC development in autoimmune thyroiditis (33), and Wen demonstrated that TPOAb are associated with a lower incidence of lymph node metastases (30).

This study has several limitations. First, this is a unicentric, retrospective study. Then, not all the patients underwent a complete CLND; thus, it is possible that the real incidence of lymph node metastasis is underestimated. Patients with autoimmune thyroiditis were not differentiated based on the different antibody status but were all included in the same category, and this could invalidate our finding of autoimmune thyroiditis as a protective factor for lymph node metastasis. In addition, a separate analysis was not performed to evaluate predictive factors for central or lateral lymph node metastasis. Finally, this study demonstrates a not negligible incidence of lymph node metastasis in PTMC, but, in this work, we did not evaluate if this finding has a significant prognostic value: further studies are required to specifically develop this issue.

## CONCLUSION

Despite the fact that PTMC is considered an indolent tumor with an excellent prognosis, the incidence of lymph node metastasis is high, even in patients with clinically uninvolved lymph nodes. The size of the tumor represents the most important predictive factor for lymph node metastasis, with tumors larger than 6 mm being at a higher risk for lymph node metastasis. Further studies could question the definition of PTMC to redefine a new cut-off value in order to better discriminate tumors with aggressive behavior, which could require aggressive surgery, from indolent tumors.

## DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Indipendente AOU Cagliari, Cagliari (Italy). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

FM, FB, ML, and PC contributed to the conception and design of the study. GC and FC organized the database and acquired the data. FM and EE performed the statistical analysis. FM wrote the first draft of the manuscript. FB, ML, EE, and PC critically revised the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

## REFERENCES


1. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. *J Cancer Epidemiol.* (2013) 2013:965212. doi: 10.1155/2013/965212
2. Ward EM, Jemal A, Chen A. Increasing incidence of thyroid cancer: is diagnostic scrutiny the sole explanation? *Future Oncol.* (2010) 6:185–8. doi: 10.2217/fon.09.161
3. Cramer JD, Fu P, Harth KC, Margevicius S, Wilhelm SM. Analysis of the rising incidence of thyroid cancer using the surveillance, epidemiology and end results national cancer data registry. *Surgery.* (2010) 148:1147–52; discussion 1152–53. doi: 10.1016/j.surg.2010.10.016
4. Hedinger C, Williams ED, Sobin LH. The WHO histological classification of thyroid tumors: a commentary on the second edition. *Cancer.* (1989) 63:908–11. doi: 10.1002/1097-0142(19890301)63:5<908::aid-cncr2820630520>3.0.co;2-i
5. Schönberger J, Marienhagen J, Agha A, Rozeboom S, Bachmeier E, Schlitt H, et al. Papillary microcarcinoma and papillary cancer of the thyroid ≤1 cm: modified definition of the WHO and the therapeutic dilemma. *Nuklearmedizin.* (2007) 46:115–20; quiz N41–42. doi: 10.1160/nukmed-0059
6. 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.* (2016) 26:1–133. doi: 10.1089/thy.2015.0020
7. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. *World J Surg.* (2010) 34:1222–31. doi: 10.1007/s00268-009-0359-x
8. Wada N, Duh Q-Y, Sugino K, Iwasaki H, Kameyama K, Mimura T, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas. *Ann Surg.* (2003) 237:399–407. doi: 10.1097/01.SLA.0000055273.58908.19
9. Roh J-L, Kim J-M, Park CI. Central lymph node metastasis of unilateral papillary thyroid carcinoma: patterns and factors predictive of nodal metastasis, morbidity, and recurrence. *Ann Surg Oncol.* (2011) 18:2245–50. doi: 10.1245/s10434-011-1600-z
10. So YK, Son Y-I, Hong SD, Seo MY, Baek C-H, Jeong H-S, et al. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. *Surgery.* (2010) 148:526–31. doi: 10.1016/j.surg.2010.01.003
11. Calò PG, Conzo G, Raffaelli M, Medas F, Gambardella C, De Crea C, et al. Total thyroidectomy alone versus ipsilateral versus bilateral prophylactic central neck dissection in clinically node-negative differentiated thyroid carcinoma. A retrospective multicenter study. *Eur J Surg Oncol.* (2017) 43:126–32. doi: 10.1016/j.ejso.2016.09.017
12. Sheng L, Shi J, Han B, Lv B, Li L, Chen B, et al. Predicting factors for central or lateral lymph node metastasis in conventional papillary thyroid microcarcinoma. *Am J Surg.* (2019) 220:334–40. doi: 10.1016/j.amjsurg.2019.11.032
13. Gu J-H, Zhao Y-N, Xie R-L, Xu W-J, You D-L, Zhao Z-F, et al. Analysis of risk factors for cervical lymph node metastasis of papillary thyroid microcarcinoma: a study of 268 patients. *BMC Endocr Disord.* (2019) 19:124. doi: 10.1186/s12902-019-0450-8
14. Medas F, Canu GL, Boi F, Lai ML, Erdas E, Calò PG. Predictive factors of recurrence in patients with differentiated thyroid carcinoma: a retrospective analysis on 579 patients. *Cancers (Basel).* (2019) 11:1230. doi: 10.3390/cancers11091230
15. Calò PG, Medas F, Loi G, Erdas E, Pisano G, Nicolosi A. Differentiated thyroid cancer in the elderly: our experience. *Int J Surg.* (2014) 12:S140–3. doi: 10.1016/j.ijsu.2014.08.362
16. Chow S-M, Law SCK, Chan JKC, Au S-K, Yau S, Lau W-H. Papillary microcarcinoma of the thyroid?Prognostic significance of

lymph node metastasis and multifocality. *Cancer.* (2003) 98:31–40. doi: 10.1002/cncr.11442
17. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al. Preoperative ultrasonographic examination for lymph node metastasis: usefulness when designing lymph node dissection for papillary microcarcinoma of the thyroid. *World J Surg.* (2004) 28:498–501. doi: 10.1007/s00268-004-7192-z
18. Xiangqian Z, Chen P, Ming G, Jingtai Z, Xiukun H, Jingzhu Z, et al. Risk factors for cervical lymph node metastasis in papillary thyroid microcarcinoma: a study of 1,587 patients. *Cancer Biol Med.* (2019) 16:121. doi: 10.20892/j.issn.2095-3941.2018.0125
19. Cheng F, Chen Y, Zhu L, Zhou B, Xu Y, Chen Y, et al. Risk factors for cervical lymph node metastasis of papillary thyroid microcarcinoma: a single-center retrospective study. *Int J Endocrinol.* (2019) 2019:1–6. doi: 10.1155/2019/8579828
20. Kim SK, Park I, Woo J-W, Lee JH, Choe J-H, Kim J-H, et al. Predictive factors for lymph node metastasis in papillary thyroid microcarcinoma. *Ann Surg Oncol.* (2016) 23:2866–73. doi: 10.1245/s10434-016-5225-0
21. Lombardi CP, Bellantone R, De Crea C, Paladino NC, Fadda G, Salvatori M, et al. Papillary thyroid microcarcinoma: extrathyroidal extension, lymph node metastases, and risk factors for recurrence in a high prevalence of goiter area. *World J Surg.* (2010) 34:1214–21. doi: 10.1007/s00268-009-0375-x
22. Park JP, Roh J-L, Lee JH, Baek JH, Gong G, Cho K-J, et al. Risk factors for central neck lymph node metastasis of clinically noninvasive, node-negative papillary thyroid microcarcinoma. *Am J Surg.* (2014) 208:412–8. doi: 10.1016/j.amjsurg.2013.10.032
23. Xu Y, Xu L, Wang J. Clinical predictors of lymph node metastasis and survival rate in papillary thyroid microcarcinoma: analysis of 3607 patients at a single institution. *J Surg Res.* (2018) 221:128–34. doi: 10.1016/j.jss.2017.08.007
24. Wang M, Wu W-D, Chen G-M, Chou S-L, Dai X-M, Xu J-M, et al. Could tumor size be a predictor for papillary thyroid microcarcinoma: a retrospective cohort study. *Asian Pac J Cancer Prev.* (2015) 16:8625–8. doi: 10.7314/apjcp.2015.16.18.8625
25. Gong Y, Li G, Lei J, You J, Jiang K, Li Z, et al. A favorable tumor size to define papillary thyroid microcarcinoma: an analysis of 1176 consecutive cases. *Cancer Manag Res.* (2018) 10:899–906. doi: 10.2147/CMAR.S154135
26. Choi JB, Lee WK, Lee SG, Ryu H, Lee CR, Kang SW, et al. Long-term oncologic outcomes of papillary thyroid microcarcinoma according to the presence of clinically apparent lymph node metastasis: a large retrospective analysis of 5,348 patients. *Cancer Manag Res.* (2018) 10:2883–91. doi: 10.2147/CMAR.S173853
27. Oh H-S, Ha J, Kim HI, Kim TH, Kim WG, Lim D-J, et al. Active surveillance of low-risk papillary thyroid microcarcinoma: a multi-center cohort study in Korea. *Thyroid.* (2018) 28:1587–94. doi: 10.1089/thy.2018.0263
28. Zhao H, Li H. Meta-analysis of ultrasound for cervical lymph nodes in papillary thyroid cancer: diagnosis of central and lateral compartment nodal metastases. *Eur J Radiol.* (2019) 112:14–21. doi: 10.1016/j.ejrad.2019.01.006
29. Xue S, Wang P, Hurst ZA, Chang YS, Chen G. Active surveillance for papillary thyroid microcarcinoma: challenges and prospects. *Front Endocrinol (Lausanne).* (2018) 9:736. doi: 10.3389/fendo.2018.00736
30. Wen X, Wang B, Jin Q, Zhang W, Qiu M. Thyroid antibody status is associated with central lymph node metastases in papillary thyroid carcinoma patients with Hashimoto's thyroiditis. *Ann Surg Oncol.* (2019) 26:1751–8. doi: 10.1245/s10434-019-07256-4
31. Vasileiadis I, Boutzios G, Charitoudis G, Koukoulioti E, Karatzas T. Thyroglobulin antibodies could be a potential predictive marker for papillary thyroid carcinoma. *Ann Surg Oncol.* (2014) 21:2725–32. doi: 10.1245/s10434-014-3593-x
32. Karatzas T, Vasileiadis I, Zapanti E, Charitoudis G, Karakostas E, Boutzios G. Thyroglobulin antibodies as a potential predictive marker of papillary thyroid carcinoma in patients with indeterminate cytology. *Am J Surg.* (2016) 212:946–52. doi: 10.1016/j.amjsurg.2015.12.030
33. Paparodis R, Imam S, Todorova-Koteva K, Staii A, Jaume JC. Hashimoto's thyroiditis pathology and risk for thyroid cancer. *Thyroid.* (2014) 24:1107–14. doi: 10.1089/thy.2013.0588

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 08 September 2020
doi: 10.3389/fendo.2020.00511

# Predictive Factors of Central-Compartment Lymph Node Metastasis for Clinical N0 Papillary Thyroid Carcinoma With Strap Muscle Invasion

*Shuai Xue*[1†], *Li Zhang*[2†], *Renzhu Pang*[1], *Peisong Wang*[1], *Meishan Jin*[3], *Liang Guo*[3], *Yuhua Zhou*[3], *Bingfei Dong*[1*] and *Guang Chen*[1*]

[1] Department of Thyroid Surgery, The First Hospital of Jilin University, Changchun, China, [2] Department of Nephrology, The First Hospital of Jilin University, Changchun, China, [3] Department of Pathology, The First Hospital of Jilin University, Changchun, China

OPEN ACCESS

**Edited by:**
Christoph Reiners,
University Hospital
Würzburg, Germany

**Reviewed by:**
Yuri Nikiforov,
University of Pittsburgh, United States
Silvia Martina Ferrari,
University of Pisa, Italy

***Correspondence:**
Bingfei Dong
dongbingfei@hotmail.com
Guang Chen
jidayiyuanjzx@sina.com

[†] These authors have contributed equally to this work and share first authorship

**Specialty section:**
This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology

**Received:** 14 December 2019
**Accepted:** 25 June 2020
**Published:** 08 September 2020

**Citation:**
Xue S, Zhang L, Pang R, Wang P, Jin M, Guo L, Zhou Y, Dong B and Chen G (2020) Predictive Factors of Central-Compartment Lymph Node Metastasis for Clinical N0 Papillary Thyroid Carcinoma With Strap Muscle Invasion. Front. Endocrinol. 11:511. doi: 10.3389/fendo.2020.00511

**Background:** Papillary thyroid carcinoma (PTC) patients with anterior extrathyroidal extension (ETE) involving the strap muscle have a relatively better prognosis than those with posterior gross ETE involving the recurrent laryngeal nerve. Whether prophylactic central-compartment lymph node dissection (CLND) should be performed in PTCs with only strap muscle invasion (SMI) is still unclear.

**Methods:** A retrospective cohort study was conducted in clinical N0 (cN0) PTC patients with SMI who underwent thyroid surgery from 2009 to 2017. A total of 152 patients were included, and predictive factors of central-compartment lymph node metastasis (CLNM) were determined.

**Results:** Among the 281 PTCs patients with SMI, 152 (51.1%) did not clinically present with lymph node metastasis. Microscopic CLNM was identified in 77 (50.7%) cN0 PTC patients with SMI. According to the univariate and multivariate analyses, male patients and those aged <40 years were more likely to be diagnosed with CLNM than female patients and those aged >40 years (odds ratio [OR] = 6.22 [95% confidence interval (CI), 1.43–27.10], $p = 0.02$ vs. OR = 9.94 [95% CI, 2.79–35.44], $p = 0.00$). The CLNM positive rate of male patients aged <40 years was 87.5%, while that for female patients aged ≥55 years was 23.8%. However, risk factors associated with large-volume CLNM were not identified because of the small number of patients.

**Conclusions:** Taken together, nearly half of PTC patients with SMI did not clinically present with lymph node metastasis. Male sex and patients aged <40 years were identified as the predictive factors of CLNM in cN0 PTCs with SMI. Hence, the results of this single-center study raise the possibility that prophylactic CLND may be more often considered for younger male PTC patients with SMI.

**Keywords: predictive factors, central-compartment lymph node metastasis, clinical N0, papillary thyroid carcinoma, strap muscle invasion**

## INTRODUCTION

The incidence of papillary thyroid carcinoma (PTC) has significantly increased worldwide during the past decades (1, 2). Central-compartment lymph node metastasis (CLNM), considered a poor clinical feature, is associated with the prognosis of PTC (3, 4). Patients with >5 lymph node metastasis (LNM), are associated with structural recurrence, distant metastasis, and mortality (4, 5), even despite being micrometastases. Therefore, prophylactic central-compartment lymph node dissection (CLND) was recommended for T3 or T4 primary tumors, or if the information of LNM would be used to plan further treatment strategies, like completion thyroidectomy or radioiodine ablation (5). However, the sensitivity and specificity of ultrasonography (US) for diagnosing CLNM is poor (6, 7). Therefore, several preoperative clinical factors of CLNM for PTC have been identified by several studies, suggesting that high-risk PTCs require aggressive treatment (8, 9). However, the conflicting results from these studies contribute to different therapeutic strategies for PTC (10).

Extrathyroidal extension (ETE) is defined as a tumor spread outside of the thyroid and into the surrounding tissues (11). The degree of extrathyroidal extension (ETE) in PTC plays a significant role in recurrence and mortality (11). The American Thyroid Association guidelines recommend CLND in PTCs with gross ETE (5). Along with the degree of gross ETE, the site of the tumor gross invasion is also associated with disease outcome. However, only strap muscle invasion (SMI) has an effect on the prognosis of PTC, which has already been confirmed by a substantial amount of evidence (12–15). It was reported that DTC patients with only gross SMI had the same recurrent rate as those with microscopic ETE (12–14). Patients with anterior SMI have a relatively better prognosis compared with patients with posterior gross ETE involving the recurrent laryngeal nerve or esophagus because SMI can be easily resected with negative margins (16, 17). Hence, whether prophylactic CLND should only be performed in PTCs with only SMI is still unclear.

This study aimed to evaluate CLNM in clinical N0 (cN0) PTC with only SMI by performing a retrospective analysis of our clinical PTC cohort and identifying the clinicopathological features to predict CLNM, which may guide physicians in planning further treatment strategies.

## MATERIALS AND METHODS

### Patient Selection

This retrospective study was approved by the Institutional Review Board of the First Hospital of Jilin University, and the need for informed consent was waived. A total of 9,866 consecutive PTC patients from January 2009 to July 2017 who underwent surgery at our department were analyzed retrospectively. The inclusion criteria for patient selection were as follows: (1) patient information found in a hospital database; (2) postoperative pathological diagnosis of conventional PTC with SMI (without other gross ETEs); and (3) absence of suspicious cervical lymph nodes observed during US, computed tomography (CT), and/or fine-needle aspiration (FNA) preoperatively (cN0). The exclusion criteria were as follows: (1): age <18 years, (2) history of neck radiotherapy, and (3) history of previous thyroid surgery. Finally, 152 PTC patients with SMI were enrolled in our study. The flowchart of patient selection is shown in **Figure 1**.

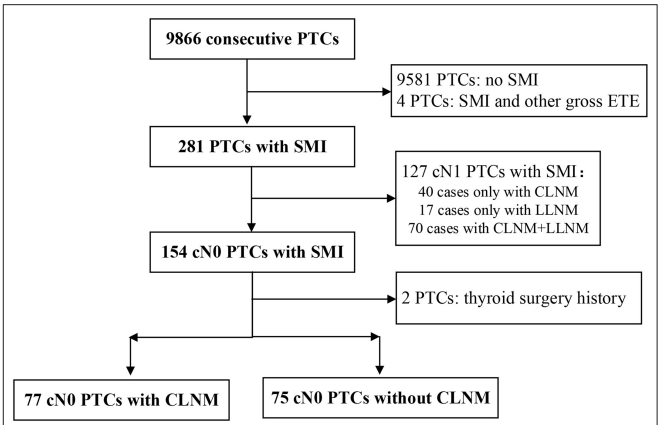


**FIGURE 1 |** Flowchart of patient selection.

### Diagnosis and Treatment

The majority of PTCs were identified by US examination, which was performed to evaluate thyroid tumor and neck lymph nodes by a trained radiologist (Y Yin) and surgeons preoperatively (SX, RP, and J Liu). FNA was recommended in patients with suspicious thyroid nodules ≥5 mm. For suspicious thyroid nodules <5 mm, after providing a full explanation of the potential risks and benefits of surgery, patients' decision on whether to undergo surgery was considered. Suspicious SMI was previously defined by US according to the following criteria: (1) a tumor was located in the anterior portion of the thyroid and (2) the thyroid capsule was disrupted by the growing tumor, or >25% of the tumor perimeter was abutting the thyroid capsule. All patients with suspicious SMI underwent neck-enhanced CT to further evaluate the SMI and cervical lymph nodes. FNA for suspicious lymph nodes was recommended when the largest diameter of the cervical lymph node was >0.8 cm and when patients presented with ≥1 malignant US/CT features (microcalcifications, cystic aspect, peripheral vascularity, hyperechogenicity, and rounded shape). The total thyroid and invaded strap muscle were dissected. Bilateral prophylactic CLND was performed (18). Radioactive iodine and thyroid-stimulating hormone-suppressive hormonal therapy were recommended to postoperative patients according to the established guidelines (5).

### Histopathological Examination

Histological specimens were examined and reviewed (19). Histopathological characteristics, including the largest tumor diameter (LTD), location of the tumor, ETE, presence of Hashimoto thyroiditis (HT), and LNM (the number and diameter), were recorded. The concordance rate between the two pathologists for the 152 enrolled patients in this study was 100%.

## Statistical Analysis

Nominal variables were described as a frequency with a percentage and a mean with a standard deviation for continuous variables. To identify the differences between groups for specific variables, the Statistical Package for the Social Sciences (SPSS) version 22 software (SPSS Inc., Chicago, IL) was used for statistical analysis. Nominal variables and continuous variables were assessed by performing Pearson's chi-squared test and Mann-Whitney *U*-test. A logistic regression model was used to evaluate the risk factors for CLNM and high-volume CLNM (≥5-mm metastatic central lymph nodes). A $p < 0.05$ was considered statistically significant (two-sided).

# RESULTS

## Baseline Characteristics

Among the 281 PTC patients with SMI, 152 (51.1%) did not clinically present with lymph node metastasis. The baseline clinicopathological and genetic characteristics of the 152 PTC patients with SMI are summarized in **Table 1**. A total of 136 (89.5%) patients were female, and the average age of all patients was 46.9 years. Ninety-five (62.5%) patients presented with a solitary tumor, while a total of 57 (37.5%) patients presented with multifocal tumors. Microscopic CLNM was identified in 77 (50.7%) cN0 PTC patients with SMI.

**TABLE 1** | Clinicopathological characteristics of cN0 PTC with SMI.

| Variables | *N* = 152 (%) |
|---|---|
| **Sex** | |
| Female | 136 (89.5) |
| Male | 16 (10.5) |
| **Age, Years** | 46.9 ± 9.5 |
| <40 | 36 (23.7) |
| 40–54 | 92 (60.5) |
| ≥55 | 24 (15.8) |
| **Bilateral** | |
| Yes | 65 (42.8) |
| No | 87 (57.2) |
| **Location of tumor** | |
| Solitary tumor | 95 (62.5) |
| Upper third | 29 (30.5) |
| Middle third | 37 (38.9) |
| Lower third | 29 (30.5) |
| Multifocal tumor | 57 (37.5) |
| In both lobes | 42 (73.7) |
| In one lobe | 15 (26.3) |
| **LTD (cm)** | 1.4 ± 0.7 |
| **HT** | |
| Yes | 55 (36.2) |
| No | 97 (63.8) |
| **CLNM** | |
| Yes | 77 (50.7) |
| No | 75 (49.3) |
| **Metastatic CLN** | 3.12 ± 2.01 |
| **Removed CLN** | 7.33 ± 4.45 |

*Categorical variables are presented as number (%, percentage). Continuous variables are presented as the average ± standard deviation. PTC, papillary thyroid carcinoma; LTD, largest tumor diameter; HT, Hashimoto's thyroiditis; CLNM, central lymph node metastasis; CLN, central lymph node.*

## Univariate and Multivariate Analysis of Risk Factors for CLNM

To identify the risk factors for CLNM in cN0 PTCs with SMI, univariate analysis for variables associated with CLNM was performed, including sex, age, bilaterality, multifocality, location of the tumor, LTD, and HT. According to the univariate and multivariate analyses, males and patients aged <40 years were more likely to be diagnosed with CLNM (odds ratio [OR] = 6.22 [95% confidence interval (CI), 1.43–27.10], $p = 0.02$; OR = 9.94 [95% CI, 2.79–35.44], $p = 0.00$) than females and patients aged >40 years, as shown in **Table 2**. The CLNM positive rate of male patients aged <40 years was 87.5%, while it was only 23.8% in female patients aged ≥55 years, as indicated in **Figure 2**.

## Univariate and Multivariate Analysis of Risk Factors for Large-Volume CLNM

To identify the risk factors for large-volume CLNM in cN0 PTCs with SMI, univariate analysis for variables associated with large-volume CLNM was performed, including sex, age, bilaterality, multifocality, location of the tumor, LTD, and HT. According to the univariate and multivariate analyses, risk factors associated with large-volume CLNM were not identified, as shown in **Table 3**.

# DISCUSSION

To the best of our knowledge, this is the first paper to determine the risk factors for CLNM in cN0 PTCs with SMI. In our 152 PTC patients with SMI, only 77 of the 152 patients (50.7%) presented with microscopic CLNM. Moreover, only 18 patients (11.8%) were reported to have large-volume CLNM (≥5-mm metastatic central lymph nodes). Furthermore, male sex and patients aged <40 years were identified as the risk factors for CLNM in cN0 PTCs with SMI.

It has been well-known that prognosis is worse in patients with gross ETE than in those with microscopic local invasion (11). However, SMI has little effect on the outcome of PTC patients, which has already been confirmed by a substantial amount of evidence (12, 16). Moran et al. reported that non-metastatic differentiated thyroid cancer patients with SMI shared similar locoregional recurrence-free rates with those with microscopic ETE (20). Compared with patients with gross ETE in the trachea, esophagus, and recurrent laryngeal nerve, patients with anterior SMI had a relatively better outcome because the invaded strap muscle can be resected easily with negative margins (17, 21, 22). Accordingly, some researchers recommended that the actual effects of SMI should be reevaluated and revised in future staging systems.

Whether routine prophylactic CLND should only be performed in PTCs with only SMI has remained controversial. The potential benefits of performing routine prophylactic

**TABLE 2 |** Univariate and multivariate analysis of clinicopathological characteristics for CLNM in cN0 PTCs with SMI.

| Variables | CLNM (+) | CLNM (-) | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | *n* = 77,% | *n* = 75,% | Odd ratio (95% CI) | *P*-value | Odd ratio (95% CI) | *P*-value |
| **Sex** | | | | | | |
| Female | 64 (83.1) | 72 (96.0) | 1 (reference) | | 1 (reference) | |
| Male | 13 (16.9) | 3 (4.0) | 4.88 (1.33–17.88) | 0.02 | 6.22 (1.43–27.10) | 0.02 |
| **Age, Years** | | | | | | |
| <40 | 27 (35.1) | 9 (12.0) | 7.29 (2.29–23.22) | 0.00 | 9.94 (2.79–35.44) | 0.00 |
| 40–54 | 43 (55.8) | 49 (65.3) | 2.13 (0.81–5.63) | 0.13 | 2.65 (0.92–7.65) | 0.07 |
| ≥55 | 7 (9.1) | 17 (22.7) | 1 (reference) | | 1 (reference) | |
| **Bilateral** | | | | | | |
| Yes | 36 (46.8) | 29 (38.7) | 1.39 (0.73–2.66) | | 1.51 (0.65–3.52) | |
| No | 41 (53.2) | 46 (61.3) | 1 (reference) | 0.31 | 1 (reference) | 0.34 |
| **Multifocality** | | | | | | |
| Yes | 32 (41.6) | 25 (33.3) | 1.42 (0.73–2.75) | | 1.72 (0.71–4.18) | |
| No | 45 (58.4) | 50 (66.7) | 1 (reference) | 0.30 | 1 (reference) | 0.23 |
| **Location of tumor with SMI** | | | | | | |
| Upper third | 17 (22.1) | 22 (29.3) | 1 (reference) | | 1 (reference) | |
| Middle third | 33 (42.9) | 30 (40.0) | 1.42 (0.64–3.18) | 0.39 | 1.31 (0.52–3.26) | 0.57 |
| Lower third | 27 (35.0) | 23 (30.7) | 1.52 (0.65–3.53) | 0.33 | 1.87 (0.73–4.76) | 0.19 |
| **LTD (mm)** | | | | | | |
| ≤10 | 22 (28.6) | 27 (36.0) | 1 (reference) | | 1 (reference) | |
| >10 | 55 (71.4) | 48 (64.0) | 1.41 (0.71–2.78) | 0.33 | 2.03 (0.92–4.49) | 0.08 |
| **HT** | | | | | | |
| Yes | 30 (39.0) | 25 (33.3) | 1.28 (0.66–2.48) | | 1.44 (0.68–3.02) | |
| No | 47 (61.0) | 50 (66.7) | 1 (reference) | 0.47 | 1 (reference) | 0.34 |

*CLNM, central lymph node metastasis; PTC, papillary thyroid carcinoma; SMI, strap muscle invasion; LTD, largest tumor diameter; HT, Hashimoto's thyroiditis.*

CLND, such as better risk stratification of recurrence according to micrometastatic central lymph nodes and lower thyroglobulin levels after operation, should be balanced by the potential risks, such as permanent hypoparathyroidism (23, 24). Hence, a number of researchers believed that prophylactic CLND was an optimal treatment for cN0 PTCs with risk factors (25). Additionally, we previously summarized a total of 1,555 cN0 PTC patients and identified that male sex and younger age were considered as the risk factors for CLNM (25). Andrew MT also reported that younger age and male sex were the strongest predictive factors for CLNM in PTC cases, which is consistent with our results (26). Regarding papillary thyroid microcarcinoma (PTMC), multiple studies have also found that male sex and younger age were associated with CLNM (27, 28). Moreover, large-volume CLNM was more frequently observed in younger and male PTMC patients than in older and female PTMC patients (29). Considering the significant number of debates on prophylactic CLND, it is recommended only in PTC patients with some risk factors. In our study, only 50.7% of cN0 PTC patients with SMI presented with microscopic CLNM. Furthermore, the CLNM positive rate of male patients aged <40 years was 87.5%. Accordingly, prophylactic CLND may be more often considered for younger male PTC patients with SMI.

This study has several limitations. First, this study was a retrospective single-center study, which may limit the generalization of the findings on a broader scale because of selection bias. Hence, prospective studies with a randomized controlled selection might be required. Second, considering the small number of cN0 PTC with SMI, predictive factors may be generated using a multivariate logistic regression model with some biases. Finally, the difference of disease outcome between SMI patients with and without CLNM was not reported in our study because of the lack of follow-up data. Despite these limitations, our study was the first study to analyze the risk factors

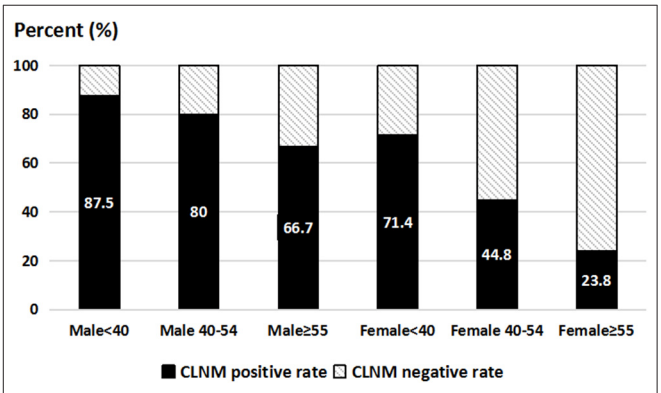


**FIGURE 2 |** Central-compartment lymph node metastasis rate according to sex and age.

**TABLE 3 |** Univariate and multivariate analysis of clinicopathological characteristics for large volume CLNM in cN0 PTCs with SMI.

| Variables | Large volume CLNM | Small volume CLNM | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | *n* = 18,% | *n* =134,% | Odd ratio (95% CI) | *P*-value | Odd ratio (95% CI) | *P*-value |
| **Sex** | | | | | | |
| Female | 14 (77.8) | 122 (91.0) | 1 (reference) | | 1 (reference) | |
| Male | 4 (22.2) | 12 (9.0) | 2.90 (0.82–10.24) | 0.10 | 2.30 (0.59–8.93) | 0.23 |
| **Age, Years** | | | | | | |
| <40 | 7 (38.9) | 29 (21.6) | 0.67 (0.16–2.73) | 0.57 | 0.63 (0.15–2.76) | 0.54 |
| 40–54 | 8 (44.4) | 84 (62.7) | 1.69 (0.39–7.31) | 0.48 | 1.57 (0.34–7.18) | 0.56 |
| ≥55 | 3 (16.7) | 21 (15.7) | 1 (reference) | | 1 (reference) | |
| **Bilateral** | | | | | | |
| Yes | 11 (61.1) | 57 (42.5) | 1.08 (0.40–2.91) | | 1.94 (0.56–6.72) | |
| No | 7 (38.9) | 77 (57.5) | 1 (reference) | 0.88 | 1 (reference) | 0.30 |
| **Multifocality** | | | | | | |
| Yes | 6 (33.3) | 51 (38.1) | 0.81 (0.29–2.30) | | 0.67 (0.19–2.39) | |
| No | 12 (66.7) | 83 (61.9) | 1 (reference) | 0.70 | 1 (reference) | 0.54 |
| **Location of tumor with SMI** | | | | | | |
| Upper third | 4 (22.2) | 35 (26.1) | 1 (reference) | | 1 (reference) | |
| Middle third | 8 (44.4) | 55 (41.1) | 1.27 (0.36–4.55) | 0.71 | 1.30 (0.33–5.05) | 0.71 |
| Lower third | 6 (33.3) | 44 (32.8) | 1.19 (0.31–4.56) | 0.80 | 1.23 (0.31–5.00) | 0.77 |
| **LTD (mm)** | | | | | | |
| ≤10 | 7 (38.9) | 42 (31.3) | 1 (reference) | | 1 (reference) | |
| >10 | 11 (61.1) | 92 (68.7) | 0.72 (0.26–1.98) | 0.52 | 0.70 (0.23–2.11) | 0.53 |
| **HT** | | | | | | |
| Yes | 5 (27.8) | 50 (37.3) | 0.65 (0.22–1.92) | | 0.65 (0.21–2.00) | |
| No | 13 (72.2) | 84 (62.7) | 1 (reference) | 0.43 | 1 (reference) | 0.45 |

*CLNM, central lymph node metastasis; PTC, papillary thyroid carcinoma; SMI, strap muscle invasion; LTD, largest tumor diameter; HT, Hashimoto's thyroiditis.*

of CLNM in cN0 PTC with SMI. Furthermore, sex and age can be easily identified preoperatively. It may have potential significant implications for prophylactic CLND in cN0 PTCs with SMI.

## CONCLUSION

In conclusion, nearly half of PTC patients with SMI did not clinically present with lymph node metastasis. Male sex and patients aged <40 years were identified as the predictive factors of CLNM in cN0 PTCs with SMI. The results of this single-center study suggest the possibility that prophylactic CLND may be more often considered for younger male PTC patients with SMI.

## DATA AVAILABILITY STATEMENT

The datasets analyzed in this article are not publicly available. Requests to access the datasets should be directed to Guang Chen, jidayiyuanjzx@sina.com.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board of the 1st Hospital of the Jilin University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## FUNDING

This study was supported by the Natural Science Foundation of Jilin Province (20180101138JC).

## REFERENCES

1. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. *JAMA.* (2017) 317:1338–48. doi: 10.1001/jama.2017.2719
2. Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. *Nat Rev Endocrinol.* (2016) 12:646–53. doi: 10.1038/nrendo.2016.110
3. Leboulleux S, Rubino C, Baudin E, Caillou B, Hartl DM, Bidart JM, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond

the thyroid capsule at initial diagnosis. *J Clin Endocrinol Metab.* (2005) 90:5723–9. doi: 10.1210/jc.2005-0285
4. Randolph GW, Duh QY, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid.* (2012) 22:1144–52. doi: 10.1089/thy.2012.0043
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.* (2016) 26:1–133. doi: 10.1089/thy.2015.0020
6. Kim E, Park JS, Son K-R, Kim J-H, Jeon SJ, Na DG. Preoperative diagnosis of cervical metastatic lymph nodes in papillary thyroid carcinoma: comparison of ultrasound, computed tomography, and combined ultrasound with computed tomography. *Thyroid.* (2008) 18:411–8. doi: 10.1089/thy.2007.0269
7. Ahn JE, Lee JH, Yi JS, Shong YK, Hong SJ, Lee DH, et al. Diagnostic accuracy of CT and ultrasonography for evaluating metastatic cervical lymph nodes in patients with thyroid cancer. *World J Surg.* (2008) 32:1552–8. doi: 10.1007/s00268-008-9588-7
8. Zhang L, Wei W-j, Ji Q-h, Zhu Y-x, Wang Z-y, Wang Y, et al. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1,066 patients. *J Clin Endocrinol Metab.* (2012) 97:1250–7. doi: 10.1210/jc.2011-1546
9. So YK, Son YI, Hong SD, Seo MY, Baek CH, Jeong HS, et al. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. *Surgery.* (2010) 148:526–31. doi: 10.1016/j.surg.2010.01.003
10. Barczynski M, Konturek A, Stopa M, Nowak W. Prophylactic central neck dissection for papillary thyroid cancer. *Br J Surg.* (2013) 100:410–8. doi: 10.1002/bjs.8985
11. Radowsky JS, Howard RS, Burch HB, Stojadinovic A. Impact of degree of extrathyroidal extension of disease on papillary thyroid cancer outcome. *Thyroid.* (2014) 24:241–4. doi: 10.1089/thy.2012.0567
12. Song E, Lee YM, Oh HS, Jeon MJ, Song DE, Kim TY, et al. A relook at the T stage of differentiated thyroid carcinoma with a focus on gross extrathyroidal extension. *Thyroid.* (2019) 29:202–8. doi: 10.1089/thy.2018.0300
13. Tam S, Amit M, Boonsripitayanon M, Busaidy NL, Cabanillas ME, Waguespack SG, et al. Effect of tumor size and minimal extrathyroidal extension in patients with differentiated thyroid cancer. *Thyroid.* (2018) 28:982–90. doi: 10.1089/thy.2017.0513
14. Park SY, Kim HI, Kim JH, Kim JS, Oh YL, Kim SW, et al. Prognostic significance of gross extrathyroidal extension invading only strap muscles in differentiated thyroid carcinoma. *Br J Surg.* (2018) 105:1155–62. doi: 10.1002/bjs.10830
15. Jung SP, Kim M, Choe JH, Kim JS, Nam SJ, Kim JH. Clinical implication of cancer adhesion in papillary thyroid carcinoma: clinicopathologic characteristics and prognosis analyzed with degree of extrathyroidal extension. *World J Surg.* (2013) 37:1606–13. doi: 10.1007/s00268-013-2034-5
16. Shaha AR. Extrathyroidal extension-what does it mean. *Oral Oncol.* (2017) 68:50–2. doi: 10.1016/j.oraloncology.2017.03.008
17. Wang LY, Nixon IJ, Patel SG, Palmer FL, Tuttle RM, Shaha A, et al. Operative management of locally advanced, differentiated thyroid cancer. *Surgery.* (2016) 160:738–46. doi: 10.1016/j.surg.2016.04.027
18. Xue S, Wang P, Zhang Q, Yin Y, Guo L, Wang M, et al. Routine lateral level V dissection may not be necessary for papillary thyroid microcarcinoma with lateral lymph node metastasis: a retrospective study of 252 cases. *Front Endocrinol.* (2019) 10:558. doi: 10.3389/fendo.2019.00558
19. Xue S, Zhang L, Wang P, Liu J, Yin Y, Jin M, et al. Predictive factors of recurrence for multifocal papillary thyroid microcarcinoma with Braf(v600e) mutation: a single center study of 1,207 Chinese patients. *Front Endocrinol.* (2019) 10:407. doi: 10.3389/fendo.2019.00407
20. Amit M, Boonsripitayanon M, Zafereo ME. ASO author reflections: strap muscle invasion does not influence recurrence and survival in patients with differentiated thyroid cancer. *Ann Surg Oncol.* (2018) 25:892–3. doi: 10.1245/s10434-018-6816-8
21. Price DL, Wong RJ, Randolph GW. Invasive thyroid cancer: management of the trachea and esophagus. *Otolaryngol Clin North Am.* (2008) 41:1155–68. doi: 10.1016/j.otc.2008.08.002
22. Perrier ND, Brierley JD, Tuttle RM. Differentiated and anaplastic thyroid carcinoma: major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin.* (2018) 68:55–63. doi: 10.3322/caac.21439
23. Henry JF, Gramatica L, Denizot A, Kvachenyuk A, Puccini M, Defechereux T. Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma. *Langenbeck's Archiv Surg.* (1998) 383:167–9. doi: 10.1007/s004230050111
24. Hughes DT, White ML, Miller BS, Gauger PG, Burney RE, Doherty GM. Influence of prophylactic central lymph node dissection on postoperative thyroglobulin levels and radioiodine treatment in papillary thyroid cancer. *Surgery.* (2010) 148:1100–6. doi: 10.1016/j.surg.2010.09.019
25. Xue S, Wang P, Liu J, Li R, Zhang L, Chen G. Prophylactic central lymph node dissection in cN0 patients with papillary thyroid carcinoma: a retrospective study in China. *Asian J Surg.* (2016) 39:131–6. doi: 10.1016/j.asjsur.2015.03.015
26. Thompson AM, Turner RM, Hayen A, Aniss A, Jalaty S, Learoyd DL, et al. A preoperative nomogram for the prediction of ipsilateral central compartment lymph node metastases in papillary thyroid cancer. *Thyroid.* (2014) 24:675–82. doi: 10.1089/thy.2013.0224
27. 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.* (2016) 26:807–15. doi: 10.1089/thy.2015.0429
28. Kim JY, Jung EJ, Park T, Jeong SH, Jeong CY, Ju YT, et al. Impact of tumor size on subclinical central lymph node metastasis in papillary thyroid microcarcinoma depends on age. *World J Surg Oncol.* (2015) 13:88. doi: 10.1186/s12957-015-0478-9
29. Oh HS, Park S, Kim M, Kwon H, Song E, Sung TY, et al. Young age and male sex are predictors of large-volume central neck lymph node metastasis in clinical N0 papillary thyroid microcarcinomas. *Thyroid.* (2017) 27:1285–90. doi: 10.1089/thy.2017.0250

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

REVIEW
published: 06 October 2020
doi: 10.3389/fendo.2020.571421

# Early Diagnosis of Low-Risk Papillary Thyroid Cancer Results Rather in Overtreatment Than a Better Survival

*Jolanta Krajewska[1]*, Aleksandra Kukulska[1,2], Malgorzata Oczko-Wojciechowska[3], Agnieszka Kotecka-Blicharz[1], Katarzyna Drosik-Rutowicz[1,2], Malgorzata Haras-Gil[1], Barbara Jarzab[1] and Daria Handkiewicz-Junak[1]*

[1] Department of Nuclear Medicine and Endocrine Oncology, M.Sklodowska-Curie National Research Institute of Oncology Gliwice Branch, Gliwice, Poland, [2] Radiotherapy Department, M.Sklodowska-Curie National Research Institute of Oncology Gliwice Branch, Gliwice, Poland, [3] Department of Genetic and Molecular Diagnostics of Cancer, M.Sklodowska-Curie National Research Institute of Oncology Gliwice Branch, Gliwice, Poland

OPEN ACCESS

**Edited by:**
Christoph Reiners,
University Hospital Würzburg,
Germany

**Reviewed by:**
Rosario Le Moli,
University of Catania, Italy
Pasqualino Malandrino,
University of Catania, Italy

***Correspondence:**
Jolanta Krajewska
jolanta.krajewska@io.gliwice.pl

**Specialty section:**
This article was submitted to Cancer Endocrinology, a section of the journal Frontiers in Endocrinology

**Received:** 10 June 2020
**Accepted:** 14 September 2020
**Published:** 06 October 2020

**Citation:**
Krajewska J, Kukulska A, Oczko-Wojciechowska M, Kotecka-Blicharz A, Drosik-Rutowicz K, Haras-Gil M, Jarzab B and Handkiewicz-Junak D (2020) Early Diagnosis of Low-Risk Papillary Thyroid Cancer Results Rather in Overtreatment Than a Better Survival. Front. Endocrinol. 11:571421. doi: 10.3389/fendo.2020.571421

We are witnessing a rapid worldwide increase in the incidence of papillary thyroid carcinoma (PTC) in the last thirty years. Extensive implementation of cancer screening and wide availability of neck ultrasound or other imaging studies is the main reason responsible for this phenomenon. It resulted in a detection of a growing number of clinically asymptomatic PTCs, mainly low-risk tumors, without any beneficial impact on survival. An indolent nature of low-risk PTC, particularly papillary thyroid microcarcinoma (PTMC), and the excellent outcomes raise an ongoing discussion regarding the adequacy of treatment applied. The question of whether PTMC is overtreated or not is currently completed by another, whether PTMC requires any treatment. Current ATA guidelines propose less extensive preoperative diagnostics and, if differentiated thyroid cancer is diagnosed, less aggressive surgical approach and limit indications for postoperative radioiodine therapy. However, in intrathyroidal PTMCs in the absence of lymph node or distant metastases, active surveillance may constitute alternative management with a low progression rate of 1%–5% and without any increase in the risk of poorer outcomes related to delayed surgery in patients, in whom it was necessary. This review summarizes the current knowledge and future perspectives of active surveillance in low-risk PTC.

**Keywords: papillary thyroid cancer, low-risk thyroid cancer, overdiagnosis, overtreatment, active surveillance, papillary thyroid microcarcinoma**

## INTRODUCTION

Thyroid cancer is the most common endocrine malignancy. The vast majority of patients, more than 90%, are diagnosed with differentiated thyroid carcinoma (DTC). Among them, 89.8% have papillary thyroid carcinoma (PTC), 4.5% follicular thyroid carcinoma, and 1.8% Hurthle cell carcinoma. The remaining cases are diagnosed with medullary thyroid carcinoma (1.6%) or anaplastic thyroid carcinoma (0.8%) (1).

We are witnessing a rapid global increase in the number of detected thyroid carcinomas in the last thirty years. Its incidence, relatively stable until the early 1990s, has nearly tripled in the United States since

1975, from 4.9 to 14.3/100,000. Interestingly, an absolute increase in women was almost four times greater than in men. Similar data come from European registries (2–4). For example, in Switzerland, the age-standardized incidence of thyroid cancer increased from 5.9 to 11.7/100,000 in women and 2.7 to 3.9/100,000 in men (2). The most spectacular data come from South Korea, where thyroid cancer incidence changed in women from 10.6/100,000 in 1996 up to 111.3/100,000 in 2010 (5). Currently, thyroid carcinoma is the most common cancer in Korean women. It has been estimated that thyroid cancer will be the four most common malignancy by 2030 (6). However, this phenomenon concerns only PTC as the number of other histological types of thyroid cancer remains stable (2, 7).

Only 38% of thyroid cancers produce clinical symptoms such as a neck lump, throat and neck discomfort, swallowing difficulties, and rarely cough, voice change, dyspnea, or symptoms related to a metastatic disease that prompt patients to start diagnostics (8). Currently, the size of the detected PTCs decreased. Twenty-five percent of thyroid cancers, diagnosed between 1988 and 1989, had ≤ 1 cm in diameter, whereas 42% were larger than 2 cm. In 2008-2009, the number of diagnosed tumors > 2 cm was 33%, whereas the smaller ones ≤ 1 cm 39% (7). Small intrathyroidal PTC ≤1 cm represents between 23% and 51% of all thyroid cancers (8–12), identified mainly by neck ultrasound or found in at least 10% of thyroids removed for benign conditions (13). It has been demonstrated that even 71% of PMTCs were incidentally identified in histopathological material after thyroid surgery (14). PMTC was diagnosed in 2%–15.2% of cases of multinodular goiter (14).

Conversely, thyroid cancer-related mortality is somewhat stable (15) and ranges between 0.4 and 0.6 deaths/100,000 persons (16, 17) or even slightly decreased (2). The results of the most recent international age-period-cohort analysis showed that the long-term declines in thyroid cancer mortality were accompanied by decreases over calendar periods and birth control, indirectly confirming the critical role of overdiagnosis in thyroid cancer epidemy (17). However, according to the data concerning the last decade, a slight increase in the mortality rate from 0.4 per 100,000 person-years in 1994–1997 up to 0.46 per 100,000 person-years in 2010–2013 (18), first in men and next in women is noticed in the USA, the UK, some European countries (Spain, Germany, Italy), Australia, and in Japanese men (19). This increase in mortality rate is higher or restricted to patients above 40 years of age (19). Likewise, the number of incidentally detected DTCs in an autopsy carried out in patients died due to other reasons, without known thyroid pathology, has remained unchanged since 1970 (20). The prevalence of incidental DTC depends on the way of thyroid examination on autopsy. Based on the meta-analysis of 35 studies involving 12,834 autopsies, it was 4.1% for the partial examination and 11.2% for the whole examination of the thyroid gland (20). Similar data were provided by a systematic review of 15 papers, published between 1969 and 2005. Latent PTC was found in 989 out of 8,619 autopsies (21). The highest prevalence (35.6%) of occult PTC was found in the Finish population (22). These data clearly demonstrate not only the indolent nature of PTC but also prove the lack of meaningful health consequences related to these tumors.

Papillary thyroid microcarcinoma (PTMC) is a small thyroid malignancy measuring ≤1 cm. An intrathyroidal PTMC without nodal and distant metastases is recognized as a very low-risk thyroid carcinoma. The tumor diameter is frequently less than 2 mm, as observed in 60% of patients (13). However, according to other data, it may range from 4.1mm to 8 mm in 35.2%–79% of cases (14). Such lesions are usually detected either by imaging procedures or through a histopathological examination of the thyroid gland operated due to benign disease. A meaningful percentage of the occult PTMC (33%–79%), found in autopsies, was smaller than 1 mm. Twenty-seven up to fifty percent were multifocal lesions (13), whereas extrathyroidal extension was observed in 25.7% of cases (14). Lymph node metastases occurred in 4.4% of patients with tumor diameter ≤5 mm. This percentage was a bit higher in tumors >5 and >8 mm. Lymph node metastases at diagnosis also correlated with nonincidental tumors, extracapsular invasion, the follicular PTC variant, or presence of Hashimoto thyroiditis (14). Similarly, according to an analysis of 1,066 patients, the male gender, younger age ≤ 45 years, multifocality, extrathyroidal extension, and larger primary tumor size > 6 mm were risk factors for lymph node metastases (23). Distant metastases at initial presentation occurred in a meager percentage of patients—0.37% (14).

PTMC represents an indolent type of thyroid carcinoma characterized by a very low mortality risk of less than 1% after 20 years following thyroid surgery (24). No differences in mortality risk were noticed between PTMC patients with incidental and non-incidental thyroid tumors (25). More importantly, no deaths were reported in nontreated patients subjected to active surveillance programs (26–28). The risk of recurrence is also extremely low, ranges between 1% and 5%, regardless of the presence of palpable lymph nodes at diagnosis. Extrathyroidal extension, large lymph node metastases ≥ 2 cm, and poorly differentiated component were risk factors of unfavorable outcomes in symptomatic PTMC (29). This risk is even lower <1% if palpable lymph nodes are excluded (13). Data obtained in a meta-analysis, published in 2008, showed the risk of local/nodal recurrence of 2.4% (231 out of 9,379 analyzed patients), whereas distant metastases were reported in 26/9,379 cases (0.27%) (14). The risk of local recurrence was significantly higher in younger patients (< 45 years), in clinically overt carcinomas, in case of multifocal tumors and the presence of lymph node metastases at diagnosis (14). According to another systemic review and meta-analysis comprising 854 patients with incidental PTMC and 2,669 patients with non-incidental PTMC it was demonstrated that the recurrence rate was significantly lower for incidental tumors (0.5%) compared to non-incidental ones (7.9%) (30). However, nor age, neither sex, size, tumor multifocality, lymph node involvement, and treatment modality were considerably associated with disease relapse (30).

## IS OVERDIAGNOSIS THE MAIN REASON OF A GROWING INCIDENCE OF LOW-RISK PTC?

Cancer overdiagnosis, by definition, "occurs if the disease is diagnosed correctly, but the diagnosis produces an unfavorable balance between benefits and harms" (31). One shall distinguish

an overdiagnosis from a false-positive result. According to Carter and Barratt, a false positive diagnosis concerns a patient who is incorrectly informed that may have cancer (31). The question of whether we face the apparent or true increase in thyroid cancer incidence is still open. The analysis of new DTC cases registered in the SEER database, diagnosed between 1988 and 2005, showed an increase not only of PTMCs but also of more advanced tumors > 4 cm in diameter and those with distant metastases (15). Similar data were obtained for children, adolescents, and young adults. Significant increasing trends were noticed for small PTCs <5 mm, 5–9 mm, 10–19 mm, as well as for tumors larger than 20 mm (32). Such findings may speak for a true increase. One of the most recent analyses demonstrated an increase in PTC incidence during 2000–2016 in women aged 20–29 years and during 2000–2012 in women aged 30–39 years, whereas between the years 2012–2016, PTC incidence stabilized in a group aged 30–39 years or even decreased in a group aged 40–49 years. There were ethnic/racial differences in the analyzed groups, with the highest incidence in white and Hispanic women aged 20–29 years. (33). The authors concluded that better diagnostic scrutiny was not probably the only cause of the growing number of PTC cases. Racial disparities with the highest incidence among white persons were also reported by the Marcadis group (34).

As the thyroid cancer increase almost exclusively concerns PTC, Pellegriti et al. (35) considered a possible role of specific carcinogens that might favor certain molecular abnormalities, characteristic for PTC. Such a hypothesis is reflected by an increase in the number of BRAF (B-Raf-proto-oncogene, serine/threonine kinase)-mutant PTC (35). The frequency of BRAF-positive PTC differs in distinct geographical localizations, so, a potential role of dietary factors or chemical compounds has to be considered (36, 37). A two-fold higher risk of *BRAF* mutation was noticed in regions with high iodine concentration in drinking water compared to those of normal iodine concentration (38). Similarly, regarding the follicular PTC variant, an increase in the frequency of *RAS* (Rat sarcoma viral oncogene homolog) mutations was observed.

Radiation exposure due to extensive use of X-rays in medical and dental diagnostic procedures, particularly in younger age, iodine intake, different environmental factors such as pollutants, high concentration of boron, vanadium, manganese, and iron in volcanic regions, chemical factors including polybrominated diphenyl ether flame retardants (PBDEs), viruses (herpes, Epstein-Barr virus), body weight and insulin resistance, TSH level, or estrogens are among factors definitely or potentially contributed to thyroid cancer incidence (35, 36, 39).

Radiation exposure is the only factor, which role in thyroid carcinogenesis was clearly demonstrated. Depending on the modality and severity of irradiation, the thyroid damage may lead to cell death or, if less severe, may cause specific genetic abnormalities leading to thyroid carcinogenesis. (40). The thyroid is very radiosensitive, particularly at a young age, so there is an inverse relationship between the age at radiation exposure and thyroid cancer risk (41). First data demonstrating a negative impact of medical radiation exposure on the thyroid, leading to an increased risk of thyroid carcinoma, were reported in 1950. Significant growth in thyroid cancer incidence in childhood was observed after the Chernobyl Nuclear Power Plant Accident (39, 40). However, radiation exposure is not likely to be a cause of the PTC epidemic as the percentage of *RET-PTC* rearrangements, believed to be a molecular fingerprint of radiation-induced PTC, decreased (12).

The impact of other factors is not so definite and requires further studies. The role of iodine intake, although it changed the epidemiology of DTC, is still discussed. Based on available data, Zimmerman and Galetti suggested iodine deficiency as a risk factor for follicular thyroid cancer and possibly for anaplastic thyroid cancer. However, the question regarding the causal role of iodine intake in PTC is equivocal. In many countries, the introduction of iodized salt was related to an increase in PTC incidence, whereas in some countries, including Australia, the US, and Switzerland, the number of new PTCs grew despite stable or decreasing iodine intake (42). Other micro- and macronutrient factors may influence the risk of the development of thyroid cancer. Some data pointed out the relationship between thyroid cancer incidence and obesity, carbohydrate, or excess in carbohydrate accumulation, or protein consumption (35, 36, 39).

Xenobiotics, the exogenous compounds and chemicals, may also interfere with thyroid function and thereby may change DTC risk. Such so-called "endocrine disruptors" may act as competitive inhibitors of the sodium/iodide symporter (perchlorate and nitrate), inhibit thyroperoxidase (TPO) activity (isoflavones), inhibit binding of thyroid hormone to transport protein (polybrominated diphenyl ethers; PBDE), bind to thyroid hormone receptors (PBDE and bisphenol A; BPA), inhibit peripheral deiodinase activity (styrenes), or decrease the half-life thyroxine (T4) in serum (PBDE and dioxins). The exposition to these compounds may result in a decrease in serum T4 concentration and an increase in serum TSH levels. However, the question of whether they promote carcinogenesis remains open (35, 39). The polluted atmosphere, water, and soil are among other environmental factors, which role in thyroid cancer development has to be considered. The data published by Drozd et al. suggested that nitrate pollution in drinking water may modify the risk of radiation-induced childhood thyroid cancer in Belarus (37). An increased exposition to hexachlorobenzene in Spanish people leaving near an organochlorine factory was probably the reason for a high incidence of thyroid cancer (39). Another question is related to a higher risk of thyroid cancer in volcanic areas, among others in Sicily, Iceland, French Polynesia, or volcanic islands of Hawaii (36, 39). A high concentration of boron, vanadium, manganese, iron, fluorine, selenium, and different trace elements in volcanic regions act as endocrine disruptors, influence the function of the thyroid gland and may promote thyroid cancer (43). The data on the role of tobacco smoking, although it is a well-recognized risk factor in numerous malignancies, are conflicting. Some of them demonstrated even an inverse relationship between DTC and cigarette smoking (39).

The discrepancy between a growing number of low-risk PTCs and a stable number of latent PTC found in autopsies indicates

that this high incidence is related to more accurate and easily accessible diagnostic methods than reflects a real trend (4, 7, 11, 44, 45). Palpable thyroid nodules could be detected in 3%–7% of the world population. This percentage increases even up to 76% if ultrasonography is used as it is able to found lesions as small as 2 mm (36, 46). Tumors ≤ 1 cm in diameter were associated with older age (≥45 years), female sex, and a higher probability of being detected with thyroid ultrasound (9). According to the Medicare data, the number of thyroid ultrasound as initial imaging per 100,000 people has increased over time at a rate of 20.9% per year between 2002 and 2013 (10). A significant relationship between the use of thyroid ultrasound and PTC incidence in particular areas has been demonstrated (10). Clinically asymptomatic thyroid nodules are also accidentally found in up to 25% of contrast-enhanced chest computed tomography (CT), 16%–18% of neck CT or MRI (magnetic resonance imaging), and in 1%–2% of fluorodeoxyglucose (FDG) PET (positron emission tomography) scans (47).

The patients more frequently tested by routine medical procedures are diagnosed with more thyroid cancers (48). Interestingly, it is more probable that screening programs detect slow-growing and indolent tumors than fast-growing and aggressive cancers. The time intervals between diagnostic procedures, based on the best cost-benefit ratio and least harm, are too long for aggressive tumors. On the contrary, fast-growing cancers producing symptoms are more likely to prompt a patient to contact a doctor any time (31). It has been estimated that about 11,000 cancers in women and 18,000 cancers in men are overdiagnosed in Australia each year (49). Interestingly, the screening program introduced in Fukushima after the nuclear plant accident showed thyroid cancer incidence 30 times higher than the national incidence in children and adolescents both in contaminated and non-contaminated regions (13). National screening procedures in South Korea were responsible for thyroid cancer incidence more that was 15 times greater than that in the UK and 5.6 times that of the USA (11, 50). Increasing use of thyroid sonography in the US between 2003 and 2013 detected at least 6594 thyroid cancers in adults ≥ 65 years. Patients with one or two comorbidities were more likely to be diagnosed with thyroid cancer as they more frequently had neck ultrasound (10).

Improvement of diagnostic accuracy of thyroid sonography may help to reduce the number of unnecessary fine-needle aspiration biopsies (FNAB). The goal of the recent analysis of 502 thyroid nodules was the comparison of five commonly used risk-stratification systems: American College of Radiology Thyroid Imaging Reporting and Data System (ACR TIRADS), American Thyroid Association (ATA) risk stratification, American Association of Clinical Endocrinologists (AACE), Korean Society of Thyroid Radiology (K-TIRADS) and European TIRADS (Eu-TIRADS). It was demonstrated that application of these systems resulted in the reduction of FNAB number by 17.1% up to 53.4%. The ACR TIRADS was characterized by the highest negative predictive value of 97.8%, with a false negative ratio of 2.2%. It allowed for the largest reduction of unnecessary FNABs (51).

Extensive implementation of cancer screening may lead not only to its overdiagnosis but also may exert, among others, a significant financial health-care impact as one of its consequences is an overtreatment. So, a possible way to resolve this problem is to reduce the number of new cases diagnosed, particularly very low-risk PTMC. It is reflected in the current ATA guidelines. Thyroid sonography with the assessment of cervical lymph nodes is recommended in all patients with known or suspected thyroid nodules but not as a screening procedure (52). The indications for FNAB, in turn, are limited to thyroid nodules, larger than ≥ 1 cm in the greatest dimension. What is more important, not all thyroid nodules ≥1 cm require FNAB. FNAB is recommended in nodules ≥ 1 cm only if high-risk (strong recommendation, moderate-quality evidence) or intermediate-risk (strong recommendation, low-quality evidence) sonographic features are present. If nodules have with low or very low-risk sonographic pattern, the biopsy is recommended in tumors ≥1.5 or ≥2 cm, respectively (52). It substantially differs from the Japanese attitude. At Kuma Hospital, they believe that it is better to diagnose a suspicious small nodule and discuss the FNAB result with a patient (26). Their idea is to avoid unnecessary treatment when patients contact another physician less familiar with thyroid carcinoma.

## OVERTREATMENT DOES NOT RESULT IN BETTER OUTCOMES

An indolent nature of the low-risk PTC, particularly PTMC, and the excellent outcomes, including data coming from first reports on active surveillance, raise an ongoing discussion, regarding the adequacy of treatment applied. The question of "whether PTMC is overtreated or not" is currently completed by another, "whether PTMC requires any treatment". The current ATA guidelines (52) comparing to the previous one (53) meaningfully move PTC management toward a less aggressive approach. In 2009 ATA recommended total or near-total thyroidectomy in all DTC cases > 1 cm in diameter unless there were no contraindications for such procedure. Thyroid lobectomy alone was considered as sufficient treatment only in patients with small (<1 cm), unifocal, intrathyroidal PCA in the absence of prior head and neck irradiation or radiologically or clinically evident lymph node involvement (53). In 2015, total thyroidectomy was definitely recommended only for patients with thyroid cancer >4 cm, or if gross extrathyroidal extension, clinically apparent lymph node involvement or distant metastases are present. Patients with lower local advancement, including DTC >1 and <4 cm, clinically N0, without extrathyroidal extension, may be subjected to either bilateral (total or near-total thyroidectomy) or unilateral one (thyroid lobectomy) surgical procedure (52). Regarding PTMC, the guidelines use the statement "*if surgery is chosen* for thyroid cancer <1cm without extrathyroidal extension and cN0, the initial surgical procedure should be a thyroid lobectomy unless there are clear indications to remove the contralateral lobe". Although there is no recommendation, which defines the criteria for active surveillance, such a statement may be cautiously

interpreted that ATA considers it as an option for PTMC. One may expect a more precise guideline in the next update as ATA listed active surveillance among the directions for future research.

Following the increase in thyroid cancer incidence, a growing number of thyroidectomies is observed (2). It was demonstrated that 38.2% of 2,563 patients subjected to surgery had thyroid cancer ≤1 cm in diameter (9). Moreover, more that 50%, even up to 80% of patients operated due to low-risk PTC, including tumors ≤ 2 cm in diameter, still undergo total thyroidectomy, although the risk of death from small PTC is extremely low and not influenced by the extent of surgical procedure (lobectomy vs. total thyroidectomy) (54–56). Even for larger PTC tumors, between 1 and 4 cm in adults, there were no differences in overall survival depending on the surgical approach (total thyroidectomy vs. lobectomy) (57). However, in this study, patients subjected to total thyroidectomy more frequently had multifocal tumors, extrathyroidal extension, lymph node involvement, distant metastases, positive surgical margins, and received radioiodine. Similarly, the risk of recurrence in PTMC without lymph node metastases at presentation does not differ between patients after lobectomy and total thyroidectomy (13).

The analysis of 29,512 PTMC patients, based on the SEER registry (1998–2010), does not show any significant differences in disease-specific survival between patients who underwent partial or total thyroidectomy. What is more important, PTMC patients subjected to any thyroid surgery had similar overall survival to the USA general population (58). Another study, also based on the SEER registry data, involved PTC staged T1-4N0M0, stratified by nonsurgical (1,453 patients) and surgical management (54,718 patients). Regrading younger patients (aged between 14 and 55 years) surgical and nonsurgical approach did not significantly differ in the 10-year disease-specific survival among 0–4cm PTCs, 4.1–6 cm PTCs, or even among tumors larger than 6 cm (59). Although indications for surgery in patients with larger PTCs do not seem disputable, these data clearly reflect an indolent nature of PTC. There are some published data demonstrating that patients who underwent total/near-total thyroidectomy and lymph node excision had a lower risk of recurrence. However, these differences were not significant (14). Such data raise the question of whether surgical treatment is necessary for PTMC patients?

If no other adverse features are present, radioiodine (RAI) is not recommended after lobectomy or total thyroidectomy for PTMC patients. Considering low-risk PTC patients, ATA does not routinely recommend RAI remnant ablation. Individual patient features, patient preferences, and disease follow-up implications should be involved in a decision-making process (52). Such a position results from the lack of EBM (evidence-based medicine) proofs confirming a beneficial impact of postoperative RAI treatment on disease-free and overall survival in low-risk PTC. However, this recommendation is weak and based on low-quality evidence. The recent analysis, published in 2019, which involved 32,229 PTC patients, among them 17,286 low-risk cases, demonstrated that nearly 25% (4,300) of low-risk cases still undergo RAI remnant ablation in the USA. Patients who were given RAI were younger (mean age 49.9 years), more often Hispanic or Asian, and more often insured than those who did not receive RAI. Moreover, patients treated with RAI more frequently had a total thyroidectomy and lymph node resection. Noteworthy, no patient treated with RAI died during the follow-up, whereas in the non-treated group—0.04% (5 patients) (55). Even a substantial percentage of PTMC patients (14,146 out of 60,586 analyzed cases) received postoperative RAI therapy according to the American National Cancer Data Base. These patients more often had a multifocal disease, larger tumors, Hispanic origin, low income, and were treated in non-academic centers. However, along with the increase of PTMC incidence, the number of PTMC or low-risk PTC patients treated with RAI decreased (60, 61). Currently, the probability of RAI administration in patients with localized PTC is lower if the patients are older > 65 years, had tumors <1 cm, and when they are treated in academic centers (61).

## ACTIVE SURVEILLANCE—IS IT A PROPER DIRECTION FOR PTMC?

Active surveillance consists of close monitoring of cancer without initial surgery or other treatment. One shall notice the difference between active surveillance and watchful waiting, which primarily is based on symptom management in patients who are likely to die due to other reasons (62). PTMC represents a large reservoir of subclinical thyroid cancer. According to Leboulleux et al. occult PTMC may "affect roughly 20 million adults in the USA and 48 million in Europe" (13). It is unlikely that its indolent biological behavior, discussed above, will change over time. Thus, the idea of active surveillance seems to be an option for very low-risk small PTCs.

The history of active surveillance started more than 25 years ago in Japan. Based on a high incidence of latent thyroid cancer found in autopsies and on the results of screening procedures detecting thyroid carcinoma in 3.5% of otherwise healthy Japanese women, Dr. Akira Miyauchi hypothesized that the majority of low-risk PTCs did not progress at all or showed a very slow progression. He assumed that 1. active surveillance could identify a small percentage of PTMC that progressed and developed lymph node metastases, 2. delayed surgery for these PTMC did not result in poorer outcomes, 3. surgical management applied in all PTMCs did more harm than good (26).

The data on active surveillance in low-risk and very low-risk thyroid carcinoma published so far are encouraging (**Table 1**). The first retrospective report came from the Kuma Hospital in Japan, where the idea of active surveillance in thyroid carcinoma was introduced (63). One hundred sixty-two out of 732 patients diagnosed with PTMC between 1993 and 2001 chose follow-up without surgery. More than 70% of nodules remained unchanged. Only 10.2% increased by more than 10 mm, whereas lymph node metastases in the lateral neck compartment occurred in 1.2% of patients. Regarding 626

**TABLE 1** | Summary of the results of studies on active surveillance presented in this review.

| Study data | Size of thyroid nodules included | Number of patients subjected to AS | Disease progression criteria | Mean follow-up | Percentage of patients with tumor progression | Percentage of patients with LN metastases |
|---|---|---|---|---|---|---|
| Retrospective studies | | | | | | |
| Ito (Japan) (63) | PTMC | 162 | Nodule increase ≥2 mm | 47 months (18–113) | 10.2% | 1.2% |
| Ito (Japan) (27) | PTMC | 340 | Nodule increase by ≥3 mm; development of LN metastases | 74 months (18–187) | 6.4%* 15.9%** | 1.4%* 3.4%** |
| Ito (Japan) (28) | PTMC | 1,235 | Nodule increase up to 12 mm or more; development of LN metastases | 60 months (18–228) | 4.6% | 1.5% |
| Prospective studies | | | | | | |
| Sugitani (Japan) (29) | PTMC | 230 (300 nodules) | Nodule increase ≥3 mm; invasion of local structures; development of LN or distant metastases | 5 years (1–17) | 7% | 1% |
| Tuttle (USA) (64) | PTC ≤ 15 mm | 291 | Nodule increase ≥3 mm; extrathyroidal extension; invasion of local structures; development of nodal or distant metastases | 25 months (6–166) | 3.8% | 0% |
| Sakai (Japan) (65) | PTC T1bN0M0 | 61 | Nodule increase ≥3 mm; development of nodal or distant metastases | 7.4 years (0.5–25) | 7% | 3% |
| Molinaro (Italy) (66) | Bethesda V (suspicious for PTC) or VI (PTC) nodules ≤13 mm | 93 | Nodule increase by ≥3 mm; development of LN metastases | 19 months (6–54) | 2% | 1% |

*PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma; LN, lymph nodes; AS, active surveillance; *5-year follow-up; **10-year follow-up.*

operated patients, 570 persons chose surgery at diagnosis, and the remaining 56 were operated after the follow-up period. Lymphadenectomy was performed in 594 patients, and, what is surprising, lymph node metastases were diagnosed in 50.5% of them. Multifocal tumor growth was observed in 48.2% of patients. The rate of recurrence in this group was 2.7% after 5 years and 5.0% after 8 years (63). Subsequent retrospective analysis, carried out at the Kuma Hospital between the years 1993 and 2004, was published in 2010. In this paper, the outcomes of 340 PTMC patients subjected to active surveillance were compared to 1,055 patients who underwent immediate surgery. The risk of 5 and 10-year tumor enlargement by 3 mm was 6.4% and 15.9%, respectively. Lymph node metastases occurred in 1.4% of patients after 5 years and in 3.4% of patients after 10 years. The mean follow-up was 74 months (range 18–187 months). No factors related to the tumor increase or nodal metastases were found. None of the patients after delayed surgery showed PTC recurrence (27). The latest summary of active surveillance at the Kuma Hospital was published in 2014. It reported a retrospective follow-up (mean time 60 months; range 18–228) of a group of 1235 PTMC patients, who chose the observation. Only 58 (4.6%) patients showed the enlargement of the nodule. The number of patients who developed lymph node metastases was lower −19 (1.5%). The percentage of patients with progression was lowest in older patients. Age < 40 years and tumor size 9 mm or larger were independent factors related to disease progression. Importantly, there were no distant metastases or cancer-related death under this study (28).

Prospective data concerning active surveillance are scarce. After the observation of 300 asymptomatic PTMC at the Cancer Institute Hospital in Tokyo for a mean of 5 years (range 1–17) 269 tumors (90%) remained unchanged, 9 (3%) decreased, whereas the remaining 22 (7%) increased in size. Three patients (1%) with lymph node metastases and nine (4%) with tumor increase underwent surgery. Nobody had an extrathyroidal extension or developed distant metastases, as well as no postoperative recurrences, were diagnosed. On the contrary, 10-year cause-specific survival in a group with symptomatic PTMC was only 80%. (29). The authors did not clearly define which patients were considered symptomatic. One may guess that term "symptomatic PTMC" concerned patients with lymph node or distant metastases or extrathyroidal invasion confirmed by imaging studies. In another analysis, carried out in a group of 291 low-risk PTC patients with intrathyroidal tumors ≤15 mm, nodule progression by 3 mm or more were stated in 11 (3.8%) patients, with a 5-year cumulative incidence of 12.1%. No lymph node or distant metastases occurred in this group. The mean follow-up was 25 months (range 6–166 months) (64). Recently, the cut-off value of the PTC diameter qualified for active surveillance has moved toward pT1bN0M0 tumors. Japanese researchers reported the results of a prospective analysis in a group of 392 T1bN0M0 PTC patients, among whom 61 persons chose active surveillance over surgery, and compared them to 331 patients who underwent surgery. Tumor diameter ranged from 11 to 16 mm. After a mean observation of 7.4 years, four (7%) T1bN0M0 tumors increased in size, whereas two patients (3%) developed lymph node metastases. Weak calcification and rich vascularity were risk factors for tumor growth, while younger age was a predictor for lymph node metastasis (65).

First European experiences with active surveillance in PTMC come from Italy. Ninety-three patients with a thyroid nodule

≤1.3 cm and cytological diagnosis of PTC (Bethesda VI) or suspicious for PTC (Bethesda V) were enrolled in a prospective observational study with the median duration of follow-up of 19 (range 6–54) months. Clinical or sonographic evidence of extrathyroidal extension, lymph node or distant metastases, and hyperthyroidism were among the key exclusion criteria. Twenty patients dropped out of the study for personal reasons. Three percent of patients (3/93) showed PTMC progression, among them two persons—tumor increase by more than 3 mm in each dimension, and one patient lymph node metastases. All of them were diagnosed with the Bethesda V category. At the time of data cut-off, 71 patients (76%) were still in follow-up (66).

A systematic review and a meta-analysis (67), published in 2019, was based on the evaluation of 6 studies, including four presented above (27, 28, 64, 65). The pooled proportion of the tumor diameter increase and lymph node metastasis at 5 years was 5.3% and 1.6%, respectively (67). The most recent meta-analysis included 9 papers, 4,156 patients at a mean age ranged from 51 to 54 years, mainly females, among them 3,120 persons from Japan, 688 from South Korea, 291 from the United States, and 57 from Colombia. Searching criteria included relevant studies of active surveillance for low-risk PTC defined as T1a or T1b N0M0. Seven studies enrolled patients with tumors ≤ 10 mm, while the remaining two expanded size criteria up to 15 mm. The pooled data demonstrated the risk of tumor growth to be 4.4%, whereas metastatic spread to cervical lymph nodes – 1.0%. Thyroid cancer-related pooled mortality was 0.03%. The pooled percentage of delayed surgery, reported in 8 out of nine analyzed studies, was 9.9%. However, patient preference but not a disease progression was the main reason for surgery—51.9%. The recurrence rate after a delayed surgery was 1.1% only (68). Such data clearly demonstrate that active surveillance in low-risk PTC may be a safe option for the patients and does not produce any substantial risk related to a delayed surgery, in patients in whom it was necessary. We have to wait for the outcomes of other ongoing clinical trials. We may expect new EBM data sufficient to introduce active surveillance into daily clinical practice in the USA and Europe.

Younger age, mainly below 45 years, was a factor associated with PTC progression in some studies on active surveillance (28, 64, 65, 69, 70), whereas in other not (71, 72). Some sonographic features may help to predict PTC progression during active surveillance, among them weak calcification and rich vasculature (65). Kim et al. reported that sustained, high mean TSH level, above the cut-off point of 2.5 mU/L, was associated with PTMC progression during active surveillance (69). However, the earlier report did not find any significant correlation between the mean TSH level and PTMC progression (72). Hirokawa et al. analyzed pathological features of PTMC tumors that demonstrated progression or developed lymph node metastases during active surveillance ≥ 1 year. The values of Ki67 indices were above 5% and 10% in 50% and 22% of growing tumors, respectively. Simultaneously, these values were significantly higher than those observed in non-progressing tumors. Intraglandular dissemination and psammoma bodies, in turn, correlated with the occurrence of lymph node metastases (70).

Considering active surveillance, one should define its protocol, determine the duration of monitoring, identify who is an appropriate candidate, and finally, its effect on the patient's emotional health (62). One of the most critical issues is to accurately define a candidate for active surveillance to avoid overtreatment on the one hand and simultaneously not to produce any increase in the risk of cancer-related mortality. It seems evident that not all low-risk PTC patients should be subjected to active surveillance. Miyauchi et al. listed several contraindications, among them the presence of lymph node and distant metastases, suspicion of high-grade malignancy on FNAB, and some sonographic features. When the nodule is located next to the recurrent laryngeal nerve or attaches the trachea at an obtuse angle, such patients should be referred to surgery (26, 73) (**Figure 1**). On the contrary, a nearly right angle was associated with an unclear or moderate risk, whereas an acute angle between the tumor and trachea with a low risk (73). The risk of the laryngeal nerve invasion was greater in the absence of a normal thyroid rim close to the nerve location (73). However, according to the Japanese researchers, multifocal tumors and a positive family history of non-medullary thyroid carcinoma did not exclude from active surveillance (26).

In 2010 three distinct types of PTMC were proposed. Type I represented harmless, asymptomatic, incidentally identified the lowest risk PTMC. Type II involved an early stage of usual low-risk PTC, whereas type III comprised of clinically apparent high-risk PTMC. The choice of treatment strategy varied depending on the tumor type. Type I tumors qualified for active surveillance, type II for lobectomy when increasing size was observed, and type III for more aggressive treatment with total thyroidectomy and RAI (29). Unfortunately, no precise criteria for each type were given. Such a risk-stratified approach should evaluate three interrelated but distinct domains, including tumor/neck ultrasound characteristics, patient characteristics, and finally, medical team characteristics. Tumor/neck ultrasound characteristics has to consider primary tumor size, its location within the thyroid, molecular profile, and the status of cervical lymph nodes. Regarding patient characteristics, age, child-bearing potential, family history of thyroid cancer, comorbidities, patient's willingness to defer immediate surgery, and compliance with follow-up are among the factors for consideration. Medical team characteristics, in turn, is based on the availability and expertise of the multidisciplinary team, the quality of sonography, and the experience of the treating physician (74). Based on these domains and the data presented above, an ideal candidate would be an older patient, with a probable or proven solitary PTMC, characterized in sonography by a well-defined margin, confined to thyroid parenchyma, and not adjacent to the thyroid capsule. Younger patients, with multifocal disease, tumor adjacent to the thyroid capsule in noncritical locations, potentially more aggressive phenotype, or the presence of other sonographic features that make follow-up difficult (thyroiditis, non-specific lymphadenopathy, etc.) are considered as inappropriate candidates. Finally, patients with tumors showing critical subcapsular location (adjacent to the recurrent laryngeal nerve or trachea) with the evidence of extra

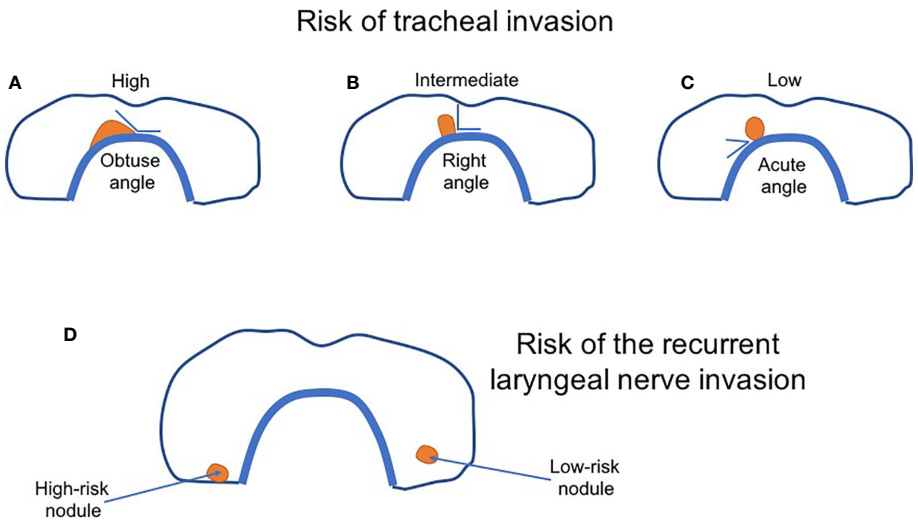


**FIGURE 1** | The scheme of sonographic classification of thyroid nodules based on the risk of tracheal and the recurrent laryngeal nerve invasion. **(A–C)** The risk of tracheal invasion depends on the angle between the nodule and tracheal wall. **(A)** High-risk nodule—an obtuse angle; **(B)** Intermediate-risk nodule—a right angle; **(C)** Low-risk nodule—an acute angle. **(D)** The risk of the laryngeal nerve invasion. Low-risk nodule (right) is surrounded by a thin of the normal thyroid. High-risk nodule (left)—no rim of the normal thyroid is observed. A nodule closely adheres to thyroid capsule and the nerve. The figure was modified by the authors based on Akira Miyauchi paper (67).

thyroid extension, metastases, or progression on serial examinations are inappropriate candidates (74).

Currently conducted a Multicenter Prospective Cohort Study of Active Surveillance on PTMC (MAeSTro study) involves adult patients, with a thyroid nodule ≤ 1 cm, diagnosed by fine-needle aspiration biopsy as Bethesda V (suspicious for thyroid cancer) or Bethesda VI (thyroid cancer). Multifocal tumors or a positive family history of non-medullary thyroid carcinoma are allowed. The infiltration of adjacent structures (trachea, esophagus, major vessels, nerves, or muscles), suspicious lymph nodes, poorly differentiated histology or a higher risk PTC variant, and Graves' disease with an indication for RAI treatment or surgery are the main exclusion criteria (75). A Canadian prospective observational study of decision-making on active surveillance for low-risk PTC consider adult patients as eligible if they have PTC ≤ 2 cm in diameter, confined to the thyroid and simultaneously not adjacent to trachea or the recurrent laryngeal nerve, without lymph node involvement, or the diagnosis of poorly differentiated or non-papillary thyroid cancer (76, 77).

Although the molecular profile of the nodule may be helpful in the risk stratification, there are no currently validated molecular risk factors used in the decision-making process qualify for active surveillance to differentiate between an early stage aggressive lesion and an indolent occult cancer (74). *BRAF* mutations are commonly observed in PTMC, with a frequency ranging between 0% and 92.6%, on average, 57.4% (78). Importantly in some papers, their occurrence in PMTC did not significantly differ from PTC. In a Korean study, it was 65.5% and 67.2%, respectively (79). However, other reports demonstrated a higher percentage of *BRAF* mutations in PTC (78). *BRAF* mutations were more prevalent in classic (43%–81% of cases) and tall cell (93%–100% of cases) PTMC variants than in follicular one (0–67% of cases) (78). According to the most recent study, published by these Korean researchers, the frequency of *BRAF* mutation was higher in PTMC > 0.5 cm than in smaller ones ≤ 0.5 cm and decreased again in PTCs > 2 cm (80). Such a high prevalence speaks against using the *BRAF* mutation as an independent prognostic or predictive factor. However, Kim and coworkers believe that BRAF status may facilitate choosing the candidates for active surveillance. Their most recent multicenter study that included 743 PTMC patients, treated with total thyroidectomy, showed a significantly higher risk of tumor recurrence in BRAF positive group than BRAF negative one, 10.8% vs. 6.4%, respectively (81). These data are concordant with a meta-analysis, which involved 2,247 PTMC patients and demonstrated an increased risk of recurrence in BRAF positive tumors (82). On the contrary, in Yabuta study, described below, the *BRAF* mutation was not a predictive factor in term of tumor behavior as in was present in 64%, 70%, and 80% of PTMC from the non-progressing group, size-increase group, and lymph node metastasis group, respectively (83).

Yabuta and coworkers analyzed the risk of PTMC progression on active surveillance with reference to the *TERT* promoter mutations. They selected three groups of patients: the non-progressing group, the size-increase group, and the lymph node metastasis group. They did not find *TERTp* mutations in any of the analyzed groups (83). However, such mutations may be incidentally present in PTMC (84), even in tumors <5 mm in diameter (80), without any significant correlation with unfavorable clinical features (85, 86).

Rodrigues and coworkers concluded their comprehensive review regarding the molecular biology of PTMC, based on currently available data, nor the *BRAF* mutation alone, neither any other molecular alternation is sufficient to predict an aggressive behavior of PTMC (78). We share their opinion. Similarly, there are also no unequivocal clinical data. Further prospective studies are necessary to resolve this question.

Another important point is to define the protocol of active surveillance. At Kuma Hospital, ultrasound examination is repeated 6 months after the initial one, and next once a year (26). Sugitani et al. proposed a follow-up with ultrasonography every 6 or 12 months. MAeSTro study started in June 2016, scheduled follow-up visits every six months during the first two years, and every year thereafter (75).

The definition of tumor progression is not less important. Kuma Hospital proposes a tumor increase by > 3 mm or the development of lymph node metastases (26). According to the MAeSTro study, an increase in the longest tumor diameter by at least 3 mm, or ≥ 2 mm in two dimensions, suspected organ involvement, or the occurrence of lymph node/distant metastases fulfills the criteria of disease progression. Similar criteria of disease progression are proposed by the Canadian study, mentioned above. An additional criterion concerns PTC growth in a location adjacent to the trachea or the recurrent laryngeal nerve (76). Tuttle et al. demonstrated that three-dimensional measurement of the tumor volume allowed for the identification of the tumor progression with the median of 8.2 months (range 3–46 months) earlier than an increase in a single diameter (64). Changes in tumor volume were also evaluated in a retrospective Korean study, carried out in 192 PTMC patients. Seventy-two patients showed an increase in tumor volume more than 50% without an increase of the longest tumor diameter ≥ 3 mm. This finding confirmed the observation published by Tuttle group. Only four patients from the Korean group had both an increase in tumor volume and in the longest dimension ≥3 mm (71).

## QUALITY OF LIFE, PSYCHOLOGICAL, AND ECONOMIC CONSIDERATIONS

The diagnosis of malignant neoplasm is not only an essential medical event, but it also concerns different economic, psychological, and sociological issues. It is of particular relevance in some malignancies, showing a growing incidence. Early detection does not result in any improvement of their curability, like in non-invasive breast, thyroid, and prostate carcinoma (49), leading to overdiagnosis. Patients overdiagnosed with thyroid cancer are harmed by the psycho-social aspect of cancer diagnosis, treatment applied, and treatment-related consequences. Rogers et al. defined ethical concerns related to thyroid cancer overdiagnosis. The way we informed a patient about the disease, treatment modalities, and possible risk is of particular relevance. We are obliged to give objective data, respect patient's autonomy, promote patient's wellbeing, avoid harm, and consider matters of justice. One should consider pain, inconvenience, and anxiety at diagnosis, short and long-term impact of therapeutic approach (postoperative transient and permanent complications, postoperative follow-up, complying with medications), worry about recurrence, threats to personal identity, social participation and relationships. Surprisingly, a thyroid cancer diagnosis may result in a significant financial disadvantage as in the USA, patients diagnosed with any cancer had a higher bankruptcy rate than people without malignant neoplasms. Other points are a considerable economic impact on health care and various conflict of interest (87).

Active surveillance has been implemented for managing low-risk prostate cancer for many years. It has risen to limit the overtreatment, the related risk, and other important consequences. The idea of its adoption for low-risk thyroid cancer has been slowly developed since 1993. The number of its supporters gradually increases (88). However, the question of whether both physicians and patients are ready for it remains open. On the one hand, active surveillance may protect a significant number of patients from surgery with its potential complications and their treatment, life-long thyroid replacement therapy, or even from RAI administration and its consequences. On the other hand, active surveillance may be related to a potential disease progression or other disadvantages, including anxiety due to untreated malignancy or the possibility of non-compliance to follow-up protocol (89).

The majority of papers analyze the outcomes of different treatment methods and other issues outstanding from the medical point of view. In contrast, the studies evaluating patient participation in the decision-making process are rarer. The choice of treatment method more frequently depends on physician decisions than on patient preference. The analysis based on the SEER registry, including 1,319 PTC patients, demonstrated that 55.8% of persons felt they did not have any choice regarding RAI administration and presented a lower satisfaction with the treatment decision. Nearly 95% of patients whose physicians recommended such therapy, were treated with RAI. On the contrary, only 22.5% of patients received postoperative RAI therapy, if their physician recommended against this treatment (90). Sawka et al. reported the results of a prospective mixed-methods study of decision making on surgery or active surveillance for low-risk PTC < 2 cm in maximum diameter. Standardized medical information was provided for all patients. Next, patients were interviewed after making the decision. Ninety-four percent of 100 patients enrolled independently chose the management for their disease, whereas the remaining persons shared the decision with their physicians. Seventy-one patients chose active surveillance, 29—immediate surgery. PTMC was more prevalent in individuals choosing active surveillance compared to patients choosing surgery, 54.9% vs. 27.6%, respectively. The vast majority of patients (96.6%) opting for surgery had postsecondary education. On the contrary, 33.8% of patients who preferred active surveillance finished their education at the high school level. Nearly all patients (98%) were satisfied with the decision they made. Perceived risk of thyroidectomy or cancer, family history of thyroid cancer or other malignancies, family

considerations, trust in physicians, and treatment timing concerning life circumstances influenced their decision (77). Korean scientists compared the impact so-called "usual care" with the "conversation aid" approach on the decision-making process concerning treatment options in a group of 278 PTMC patients. In total, 233 (84%) patients preferred active surveillance, whereas 53 (16%) individuals – thyroid surgery. Patients from the conversation aid group showed a higher probability of choosing observation than surgical treatment, 88.9% vs. 77.0%, respectively (91). These data clearly demonstrate the importance of the conversation between patients and health caregivers. The authors emphasized that conversation meant much more than information.

A widely accepted paradigm that early detection and treatment is related to a higher cancer curability is deeply rooted in patients' minds. They are much less familiar with the term "overdiagnosis" or "overtreatment". Regardless of the level of decision satisfaction in PTC patients choosing active surveillance, anxiety or emotional stress related to cancer diagnosis and resignation from surgery is reported by a majority of patients (77, 92, 93). It has been demonstrated that the so-called disease label may exert a meaningful impact on the patient's decision. An online survey, completed by 1068 predominantly healthy responders, showed their preferences between a series of two hypothetical vignettes concerning incidental detection of a small thyroid nodule, varied on disease label (cancer, tumor, or nodule), treatment (active surveillance, or lobectomy), and risk of progression/recurrence (0%, 1%, 2%, or 5%). The cancer label played a crucial role in the patient's decision, independent of proposed therapy and progression/recurrence risk (94). The role of the terminology used to define the disease was also confirmed by the results of other survey conducted in 550 Australian patients without a history of thyroid cancer. Total thyroidectomy was chosen more frequently when the term PTC was used to name the condition, compared to using papillary lesion or abnormal cells, 19.6%, 10.5%, or 10.9%, respectively (95). Similar data were reported by a discrete choice experiment also carried out in the Australian population. This study involved 2,054 participants, also without a history of thyroid carcinoma, who were randomly assigned to receive 1 of 2 groups differed with terminology used to characterize the condition: "cancer" or "lesion". Patients may decide to choose between one out of three options: thyroidectomy, lobectomy, and active surveillance. If the condition was labeled with "cancer", patients were ready to accept a higher number of adverse effects, life-long medications, calcium problems, and fatigue to avoid cancer-related death than persons which condition was called lesion (96). We agree that the terminology used by health caregivers may influence the anxiety or emotional stress related to the unfavorable diagnosis. However, we are not sure that we are allowed to use a softer term when a malignancy is diagnosed. To avoid unnecessary treatment and different psychological, physical or social consequences related to overdiagnosis, ATA does not recommend screening for thyroid nodules and a biopsy of small lesions. As it was mentioned above, Japanese doctors prefer patients to be clearly informed about the disease, prognosis and any potential risk. One should stress, ATA approach seems much acceptable for cancerphobic European patients than a Japanese one.

The terms "overdiagnosis" or "overtreatment" are raised not only by physicians or scientists. Also, patients may feel overdiagnosed or overtreated. Interesting data come from a qualitative study carried out in persons aged 21 to 75 years, in whom thyroid nodule known or suspected to be malignant was found incidentally and who questioned the treatment method proposed by their physician. Eighteen patients from this group decided not to intervene. The median of the follow-up was 40 months (range 1–88 months). Twelve out of these patients, despite significant anxiety about cancer progression, chose the observation based on understanding issues of precision in diagnostics, cancer behavior, surgical risk, medication use, and a low risk of cancer-related death. These patients felt unsupported both by medical professionals and friends. Importantly, seven patients said they wished they did not know the diagnosis, four were ambivalent, whereas only six patients were feeling glad they were informed about the disease (92). Valuable data were provided by analyzing the experience of active surveillance in Japanese patients from Kuma Hospital. Thirty-seven percent out of 243 patients rated their worry about cancer as occurring sometimes or more. Thirty-two percent reported that concern about cancer affected their mood somewhat or a lot, whereas, in 14% of patients, it affected their ability to carry out routine activities somewhat or a lot. The cancer-related worry was most potent when they found out about the diagnosis, and in 60% of patients subsequently decreased. Eighty-three percent of patients agreed or strongly agreed that choosing active surveillance was the best one they could make (93).

Quality of life shall always be taken into consideration when deciding on how to manage a patient. The evaluation of physical and psychological health is one of the outcomes of the MAeSTro study currently conduced in PTMC in South Korea. This assessment involved 203 patients choosing active surveillance and 192 individuals treated with surgery who completed questionnaires at least at two time-points. There were no differences between the groups regarding age, tumor size, TSH, thyroglobulin (Tg), and Tg antibodies level. Among persons, who opted for immediate surgery, 58 patients underwent total thyroidectomy, 133—lobectomy, 171—central lymph node dissection, and 4—lateral neck lymphadenectomy. Hypoparathyroidism and voice changes were diagnosed in 16.2% and 8.3% of patients, respectively. Regarding the active surveillance group, four patients resigned from observation due to other reasons than disease progression, mainly because of worry and anxiety. Only one patient from the active surveillance group showed disease progression. Significantly better psychological, physical, and overall health was observed during follow-up in patients who resigned from surgery (97). The risk of surgically related complications is also of great importance. All patients after total thyroidectomy require life-long thyroid hormone replacement therapy, whereas a considerable percentage of them had hypoparathyroidism or voice changes. The risk of permanent voice cord paralysis and permanent hypoparathyroidism at the

Kuma Hospital were 0.2% and 1.6%, respectively (26). It is not surprising that the group managed by immediate surgery showed a higher risk of transient vocal cord paralysis, and transient or permanent hypoparathyroidism than the active surveillance group, 4.1%, 16.7%, and 1.6% vs. 0.6%, 2.8%, and 0.08%, respectively. The ratios of patients requiring L-thyroxine supplementation and those who had the local postoperative complications were also higher in operated patients (98). The study conducted in Argentina reported an even higher risk of postoperative complications, observed in 24.4% of patients, which became permanent in 9.6% of low-risk PTC cases who did not decide for active surveillance (99). At least 1 year following surgery, patients who needed prolonged calcium and vitamin D administration demonstrated a lower quality of global health, physical, role, and emotional functioning, or insomnia compared to patients not receiving the supplementation (100). Even PTMC patients subjected to less aggressive thyroid surgery, like lobectomy, reported a worse quality of life compared to patients who decided not to operate (101). Choosing between surgery and active surveillance in PTMC, one should remember that long-term outcomes are similarly excellent in both groups. What is even more important, delayed surgery in PTMC, based on the data presented earlier in this paper, is not related to a higher risk of distant metastases or cancer-related mortality. Both approaches are associated with emotional stress and anxiety. Besides, surgery, particularly total thyroidectomy still performed in PTMC patients, may lead to permanent complications in a relatively large number of patients. Thus, the quality of life may play a crucial role in the decision-making process.

Some other issues not related to the tumor features may influence the choice between surgery and active surveillance. In some cases, insurance status exerts an impact on the extent of treatment applied (55, 102, 103). The analysis of The American College of Surgeons' National Cancer Database aimed to identify independent predictors of more intensive treatment used in PTMC patients. This study involved 190,298 PTMC individuals without nodal or distant metastases diagnosed preoperatively. The majority of patients (73.4%) from the analyzed group had private insurance. These patients were the least likely to be diagnosed with cancers showing high-risk features. On the contrary, uninsured patients more frequently had an extrathyroidal extension, lymphovascular invasion, positive surgical margins, and distant metastases. The differences between insured and noninsured patients were significant. Patients with private or public health insurance were more likely to have PTMC compared with noninsured ones. Regardless of less aggressive carcinomas, privately insured patients were more likely to be treated more extensively. Private insurance independently increased the probability of total thyroidectomy, lymphadenectomy, and postoperative RAI therapy (102). It seems indisputable that such disparities should be avoided. Valuable data come from the most recent analysis based on 34 semi-structured interviews with 12 surgeons, 12 endocrinologists, and 10 patients diagnosed with <1.5 cm PTC. Both surgeons and endocrinologists believed that overdiagnosis led to overtreatment. They considered overdiagnosis as a key issue. Biopsy, usually a reflexive or habitual action, in their opinion, was a critical point for further intervention (104). We share this opinion. When the FNAB result is positive, it usually starts the treatment process. However, the patients did not use the term overdiagnosis. In their view, the way from diagnosis to treatment seemed automatic and inevitable. Moreover, some patients and physicians prefer biopsy, regardless of the guidelines, to minimize diagnostic uncertainty. Although physicians were aware of possible overtreatment, they emphasized the difficulties in resignation from treating a diagnosed cancer. Total thyroidectomy seemed a reasonable treatment option for them (104). Similar scenarios are not rare in daily practice. We realize, changing a well-established paradigm is not easy and requires time.

Economic aspects are not less important than medical, psychological, or ethical issues. Lubitz et al. estimated that US$ 1.6 billion of the medical costs spent on thyroid cancer care in 2013 might increase up to 3.5 billion in 2030. The calculated cost includes diagnostics, surgery, adjuvant therapy for newly diagnosed patients (41%), surveillance of survivors (37%), and nonoperative death costs attributable to thyroid cancer care (22%) (105). A possible way to reduce these costs is to reduce the number of newly diagnosed very low-risk patients as well as the number of patients followed-up for a long time in referral centers (106). FNAB was related to a greater mean 12-month direct costs than observation of small incidental thyroid nodules < 2 cm in diameter, 542.47$ compared to 411.55$, respectively (107). Another way is to change treatment schemes to be equally effective but more cost-effective ones. Japanese experiences demonstrated active surveillance was more cost-effective than surgery (26). A total 10-year cost of active surveillance in patients without delayed surgery was 167,780 yen/patients, whereas in patients referred to immediate surgery, it was 794,770–1,086,780 yen/patient (108). Similar conclusions come from other reports. The non-surgical approach was more cost-effective than immediate surgery during the first 16 years after PTMC diagnosis and thereafter, regardless of patient age (< 40 and ≥ 40 years), complications, and progression rates (109). However, one may found some opposite data pointing on better cost-effectiveness of surgery compared to active surveillance in PTMC (110, 111). Australian data showed the cost of surgical therapy of 10,226 Australian dollars, whereas hypothetic active surveillance 756 Australian dollars per year. So, the cost of surgery corresponded to the cost of 16.2 years of active surveillance (111).

## CONCLUSIONS

To sum up, overdiagnosis of indolent low-risk PTCs is a global phenomenon leading to overtreatment in many cases without any beneficial effect on survival and patients' well-being. Numerous clinical trials are needed to provide the data, fulfilling evidence-based medicine criteria necessary to change our routine clinical management in PTMC patients. We may expect substantial changes in the near future. The question is whether we, both patients and physicians, are ready for it?

## AUTHOR CONTRIBUTIONS

JK: study concept, searching and literature review, writing the manuscript. AK, AK-B, KD-R, and MH-G: searching and literature review. MO-W and DH-J: literature review and writing the manuscript. BJ: study supervision, revision of the final version of the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

This work was supported by the National Centre for Research and Development project under the program "Prevention practices and treatment of civilization diseases" STRATEGMED (STRATEGMED 2/267398/4/NCBR/2015) and partially supported by The National Centre for Research and Development Grant No PBS3/B3/32/2015.

## REFERENCES

1. Noone A, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al. *SEER Cancer Statictics Review, 1975-2015, Updated September 10,2018* (2018). National Cancer Institute. Available at: https://seer.cancer.gov/archive/csr/1975_2015/results_merged/sect_26_thyroid.pdf (Accessed May 25, 2020).
2. Jegerlehner S, Bulliard J-L, Aujesky D, Rodondi N, Germann S, Konzelmann I, et al. Overdiagnosis and overtreatment of thyroid cancer: A population-based temporal trend study. *PloS One* (2017) 12:e0179387. doi: 10.1371/journal.pone.0179387
3. Dal Maso L, Panato C, Franceschi S, Serraino D, Buzzoni C, Busco S, et al. The impact of overdiagnosis on thyroid cancer epidemic in Italy,1998-2012. *Eur J Cancer (Oxford England: 1990)* (2018) 94:6–15. doi: 10.1016/j.ejca.2018.01.083
4. Dal Maso L, Lise M, Zambon P, Falcini F, Crocetti E, Serraino D, et al. Incidence of Thyroid Cancer in Italy, 1991-2005: Time Trends and Age-Period-Cohort Effects. *Ann Oncol* (2011) 22 (4):957–63. doi: 10.1093/annonc/mdq467
5. Kweon S-S, Shin M-H, Chung I-J, Kim Y-J, Choi J-S. Thyroid cancer is the most common cancer in women, based on the data from population-based cancer registries, South Korea. *Japanese J Clin Oncol* (2013) 43:1039–46. doi: 10.1093/jjco/hyt102
6. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* (2014) 74:2913–21. doi: 10.1158/0008-5472.CAN-14-0155
7. Davies L, Welch HG. Current thyroid cancer trends in the United States. *JAMA Otolaryngol – Head Neck Surg* (2014) 140:317–22. doi: 10.1001/jamaoto.2014.1
8. Rahman S, McLeod D, Pandeya N, Neale R, Bain C, Baade P, et al. Understanding Pathways to the Diagnosis of Thyroid Cancer: Are There Ways We Can Reduce Over-Diagnosis? *Thyroid: Off J Am Thyroid Assoc* (2019) 29:341–8. doi: 10.1089/thy.2018.0570
9. Esfandiari N, Hughes D, Reyes-Gastelum D, Ward K, Hamilton A, Haymart M. Factors Associated With Diagnosis and Treatment of Thyroid Microcarcinomas. *J Clin Endocrinol Metab* (2019) 104:6060–8. doi: 10.1210/jc.2019-01219
10. Haymart MR, Banerjee M, Reyes-Gastelum D, Caoili E, Norton EC. Thyroid Ultrasound and the Increase in Diagnosis of Low-Risk Thyroid Cancer. *J Clin Endocrinol Metab* (2019) 104:785–92. doi: 10.1210/jc.2018-01933
11. Lee J-H, Shin SW. Overdiagnosis and screening for thyroid cancer in Korea. *Lancet (London Engl)* (2014) 384:1848. doi: 10.1016/S0140-6736(14)62242-X
12. Jung CK, Little MP, Lubin JH, Brenner AV, Wells SAJ, Sigurdson AJ, et al. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of BRAF mutations and a sharp increase in RAS mutations. *J Clin Endocrinol Metab* (2014) 99:E276–85. doi: 10.1210/jc.2013-2503
13. Leboulleux S, Tuttle RM, Pacini F, Schlumberger M. Papillary thyroid microcarcinoma: time to shift from surgery to active surveillance? The lancet. *Diabetes Endocrinol* (2016) 4:933–42. doi: 10.1016/S2213-8587(16)30180-2
14. Roti E, degli Uberti EC, Bondanelli M, Braverman LE. Thyroid papillary microcarcinoma: a descriptive and meta-analysis study. *Eur J Endocrinol* (2008) 159:659–73. doi: 10.1530/EJE-07-0896
15. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. *Cancer* (2009) 115:3801–7. doi: 10.1002/cncr.24416
16. Lowenstein L, Basourakos S, Williams M, Troncoso P, Gregg J, Thompson T, et al. Active Surveillance for Prostate and Thyroid Cancers: Evolution in Clinical Paradigms and Lessons Learned. *Nat Rev Clin Oncol* (2019) 16 (3):168–84. doi: 10.1038/s41571-018-0116-x
17. Li M, Brito JP, Vaccarella S. Long-Term Declines of Thyroid Cancer Mortality: An International Age-Period-Cohort Analysis. *Thyroid: Off J Am Thyroid Assoc* (2020) 30:838–46. doi: 10.1089/thy.2019.0684
18. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. *JAMA* (2017) 317:1338. doi: 10.1001/jama.2017.2719
19. La Vecchia C, Negri E. Thyroid cancer: The thyroid cancer epidemic - overdiagnosis or a real increase? Nature reviews. *Endocrinology* (2017) 13:318–9. doi: 10.1038/nrendo.2017.53
20. Furuya-Kanamori L, Bell K, Clark J, Glasziou P, Doi S. Prevalence of Differentiated Thyroid Cancer in Autopsy Studies Over Six Decades: A Meta-Analysis. *J Clin Oncol : Off J Am Soc Clin Oncol* (2016) 34(30):3672–9. doi: 10.1200/JCO.2016.67.7419
21. Lee Y, Lim H, Chang H, Park C. Papillary Thyroid Microcarcinomas Are Different From Latent Papillary Thyroid Carcinomas at Autopsy. *J Korean Med Sci* (2014) 29 (5):676–9. doi: 10.3346/jkms.2014.29.5.676
22. Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer* (1985) 56:531–8. doi: 10.1002/1097-0142(19850801)56:3<531::AID-CNCR2820560321>3.0.CO;2-3
23. Zhang L, Wei W-J, Ji Q-H, Zhu Y-X, Wang Z-Y, Wang Y, et al. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. *J Clin Endocrinol Metab* (2012) 97:1250–7. doi: 10.1210/jc.2011-1546
24. Hay ID, Hutchinson ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS, et al. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. *Surgery* (2008) 144:980–7; discussion 987-8. doi: 10.1016/j.surg.2008.08.035
25. Reinke R, Mathiesen JS, Larsen SR, Hahn CH, Pedersen HB, Bentzen J, et al. A study from The Danish Thyroid Cancer Group – DATHYRCA (part of the DAHANCA organization). Incidental and Non-incidental Papillary Thyroid Microcarcinoma in Denmark 1996-2015: A national study on incidence, outcome and thoughts on active surveillance. *Cancer Epidemiol* (2019) 60:46–50. doi: 10.1016/j.canep.2019.03.011
26. Ito Y, Miyauchi A, Oda H. Low-risk papillary microcarcinoma of the thyroid: A review of active surveillance trials. *Eur J Surg Oncol* (2017) 44(3):307–15. doi: 10.1016/j.ejso.2017.03.004
27. Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg* (2010) 34:28–35. doi: 10.1007/s00268-009-0303-0
28. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid: Off J Am Thyroid Assoc* (2014) 24:27–34. doi: 10.1089/thy.2013.0367
29. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. *World J Surg* (2010) 34:1222–31. doi: 10.1007/s00268-009-0359-x
30. Mehanna H, Al-Maqbili T, Carter B, Martin E, Campain N, Watkinson J, et al. Differences in the recurrence and mortality outcomes rates of incidental and nonincidental papillary thyroid microcarcinoma: a systematic review and meta-analysis of 21 329 person-years of follow-up. *J Clin Endocrinol Metab* (2014) 99:2834–43. doi: 10.1210/jc.2013-2118
31. Carter S, Barratt A. What is overdiagnosis and why should we take it seriously in cancer screening? *Public Health Res Pract* (2017) 27 (3):2731722. doi: 10.17061/phrp2731722

32. Vergamini LB, Frazier AL, Abrantes FL, Ribeiro KB, Rodriguez-Galindo C. Increase in the incidence of differentiated thyroid carcinoma in children, adolescents, and young adults: a population-based study. *J Pediatr* (2014) 164:1481–5. doi: 10.1016/j.jpeds.2014.01.059
33. Hughes E, Rhoads A, Thomas A, Aloi J, Suhl J, Lycan T, et al. Incidence and Survival in Reproductive-Aged Women With Differentiated Thyroid Cancer: United States SEER18 2000-2016. *Thyroid* (2020). doi: 10.1089/thy.2020.0152
34. Marcadis A, Davies L, Marti J, Morris L. Racial Disparities in Cancer Presentation and Outcomes: The Contribution of Overdiagnosis. *JNCI Cancer Spectr* (2020) 4:pkaa001. doi: 10.1093/jncics/pkaa001
35. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. *J Cancer Epidemiol* (2013) 2013:965212. doi: 10.1155/2013/965212
36. Rusinek D, Chmielik E, Krajewska J, Jarzab M, Oczko-Wojciechowska M, Czarniecka A, et al. Current Advances in Thyroid Cancer Management. Are We Ready for the Epidemic Rise of Diagnoses? *Int J Mol Sci* (2017) 18:1817. doi: 10.3390/ijms18081817
37. Drozd VM, Saenko VA, Brenner AV, Drozdovitch V, Pashkevich VI, Kudelsky AV, et al. Major Factors Affecting Incidence of Childhood Thyroid Cancer in Belarus after the Chernobyl Accident: Do Nitrates in Drinking Water Play a Role? *PloS One* (2015) 10:e0137226. doi: 10.1371/journal.pone.0137226
38. Guan H, Ji M, Bao R, Yu H, Wang Y, Hou P, et al. Association of high iodine intake with the T1799A BRAF mutation in papillary thyroid cancer. *J Clin Endocrinol Metab* (2009) 94:1612–7. doi: 10.1210/jc.2008-2390
39. Marcello MA, Malandrino P, Almeida JFM, Martins MB, Cunha LL, Bufalo NE, et al. The influence of the environment on the development of thyroid tumors: a new appraisal. *Endocr-Relat Cancer* (2014) 21:T235–54. doi: 10.1530/ERC-14-0131
40. Jarzab B, Handkiewicz-Junak D, Krajewska J. Thyroid and Irradiation. In: I Huhtaniemi, L Martini, editors. *Encyclopedia of Endocrine Diseases*, *2nd ed.* Elsevier I (2018). p. 539–44. Available at: (https://www.elsevier.com/books/encyclopedia-of-endocrine-diseases/huhtaniemi/978-0-12-812199-3)
41. Farahati J, Demidchik EP, Biko J, Reiners C. Inverse association between age at the time of radiation exposure and extent of disease in cases of radiation-induced childhood thyroid carcinoma in Belarus. *Cancer* (2000) 88:1470–6. doi: 10.1002/(SICI)1097-0142(20000315)88:6<1470::AID-CNCR27>3.0.CO;2-W
42. Zimmermann MB, Galetti V. Iodine intake as a risk factor for thyroid cancer: a comprehensive review of animal and human studies. *Thyroid Res* (2015) 8:8. doi: 10.1186/s13044-015-0020-8
43. Malandrino P, Russo M, Gianì F, Pellegriti G, Vigneri P, Belfiore A, et al. Increased Thyroid Cancer Incidence in Volcanic Areas: A Role of Increased Heavy Metals in the Environment? *Int J Mol Sci* (2020) 21(10):3425. doi: 10.3390/ijms21103425
44. Cho H, Choi E, Seo D, Park B, Park S, Cho J, et al. Determinants of Undergoing Thyroid Cancer Screening in Korean Women: A Cross-Sectional Analysis From the K-Stori 2016. *BMJ Open* (2019) 9(4):e026366. doi: 10.1136/bmjopen-2018-026366
45. Udelsman R, Zhang Y. The epidemic of thyroid cancer in the United States: the role of endocrinologists and ultrasounds. *Thyroid: Off J Am Thyroid Assoc* (2014) 24:472–9. doi: 10.1089/thy.2013.0257
46. Brito J, Davies L, Zeballos-Palacios C, Morris J, Montori V. Papillary Lesions of Indolent Course: Reducing the Overdiagnosis of Indolent Papillary Thyroid Cancer and Unnecessary Treatment. *Future Oncol (London Engl)* (2014) 10(1):1–4. doi: 10.2217/fon.13.240
47. Hoang JK, Langer JE, Middleton WD, Wu CC, Hammers LW, Cronan JJ, et al. Managing incidental thyroid nodules detected on imaging: white paper of the ACR Incidental Thyroid Findings Committee. *J Am Coll Radiol: JACR* (2015) 12:143–50. doi: 10.1016/j.jacr.2014.09.038
48. Hall S, Webber C, Groome P, Booth C, Nguyen P, DeWit Y. Do doctors who order more routine medical tests diagnose more cancers? A population-based study from Ontario Canada. *Cancer Med* (2019) 8:850–9. doi: 10.1002/cam4.1925
49. Glasziou P, Jones M, Pathirana T, Barratt A, Bell K. Estimating the magnitude of cancer overdiagnosis in Australia. *Med J Aust* (2020) 212:163–8. doi: 10.5694/mja2.50455
50. Park S, Oh C-M, Cho H, Lee JY, Jung K-W, Jun JK, et al. Association between screening and the thyroid cancer "epidemic" in South Korea: evidence from a nationwide study. *BMJ (Clinical Res ed.)* (2016) 355: i5745. doi: 10.1136/bmj.i5745
51. Grani G, Lamartina L, Ascoli V, Bosco D, Biffoni M, Giacomelli L, et al. Reducing the Number of Unnecessary Thyroid Biopsies While Improving Diagnostic Accuracy: Toward the "Right" TIRADS. *J Clin Endocrinol Metab* (2019) 104(1):95–102. doi: 10.1210/jc.2018-01674
52. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 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: Off J Am Thyroid Assoc* (2015) 2016 26:1–133. doi: 10.1089/thy.2015.0020
53. Cooper DS, Doherty GM, Haugen BR, Hauger BR, Kloos RT, Lee SL, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid: Off J Am Thyroid Assoc* (2009) 19:1167–214. doi: 10.1089/thy.2009.0110
54. Welch HG, Doherty GM. Saving Thyroids — Overtreatment of Small Papillary Cancers. *New Engl J Med* (2018) 379:310–2. doi: 10.1056/NEJMp1804426
55. Moten AS, Zhao H, Willis AI. The overuse of radioactive iodine in low-risk papillary thyroid cancer patients. *Surg Oncol* (2019) 29:184–9. doi: 10.1016/j.suronc.2019.05.011
56. Nickel B, Tan T, Cvejic E, Baade P, McLeod DSA, Pandeya N, et al. Health-Related Quality of Life After Diagnosis and Treatment of Differentiated Thyroid Cancer and Association With Type of Surgical Treatment. *JAMA Otolaryngol – Head Neck Surg* (2019) 145:231–8. doi: 10.1001/jamaoto.2018.3870
57. Adam MA, Pura J, Gu L, Dinan MA, Tyler DS, Reed SD, et al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61,775 patients. "PG - 601-5; discussion 605-7." *Ann Surg* (2014) 260 (4):601–5. doi: 10.1097/SLA.0000000000000925
58. Wang TS, Goffredo P, Sosa JA, Roman SA. Papillary thyroid microcarcinoma: an over-treated malignancy? *World J Surg* (2014) 38:2297–303. doi: 10.1007/s00268-014-2602-3
59. Ho AS, Luu M, Zalt C, Morris LGT, Chen I, Melany M, et al. Mortality Risk of Nonoperative Papillary Thyroid Carcinoma: A Corollary for Active Surveillance. *Thyroid: Off J Am Thyroid Assoc* (2019) 29:1409–17. doi: 10.1089/thy.2019.0060
60. Goffredo P, Thomas S, Dinan M, Perkins J, Roman S, Sosa J. Patterns of Use and Cost for Inappropriate Radioactive Iodine Treatment for Thyroid Cancer in the United States: Use and Misuse. *JAMA Internal Med* (2015) 175 (4):638–40. doi: 10.1001/jamainternmed.2014.8020
61. Park KW, Wu JX, Du L, Leung AM, Yeh MW, Livhits MJ. Decreasing Use of Radioactive Iodine for Low-Risk Thyroid Cancer in California, 1999 to 2015. *J Clin Endocrinol Metab* (2018) 103:1095–101. doi: 10.1210/jc.2017-02269
62. Haymart M, Miller D, Hawley S. Active Surveillance for Low-Risk Cancers - A Viable Solution to Overtreatment? *New Engl J Med* (2017) 377(3):203–6. doi: 10.1056/NEJMp1703787
63. Ito Y, Uruno T, Nakano K, Takamura Y, Miya A, Kobayashi K, et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. *Thyroid: Off J Am Thyroid Assoc* (2003) 13:381–7. doi: 10.1089/105072503321669875
64. Tuttle RM, Fagin JA, Minkowitz G, Wong RJ, Roman B, Patel S, et al. Natural History and Tumor Volume Kinetics of Papillary Thyroid Cancers During Active Surveillance. *JAMA Otolaryngol – Head Neck Surg* (2017) 143:1015–20. doi: 10.1001/jamaoto.2017.1442
65. Sakai T, Sugitani I, Ebina A, Fukuoka O, Toda K, Mitani H, et al. Active Surveillance for T1bN0M0 Papillary Thyroid Carcinoma. *Thyroid: Off J Am Thyroid Assoc* (2019) 29:59–63. doi: 10.1089/thy.2018.0462
66. Molinaro E, Campopiano MC, Pieruzzi L, Matrone A, Agate L, Bottici V, et al. Active Surveillance in Papillary Thyroid Microcarcinomas is Feasible and Safe: Experience at a Single Italian Center. *J Clin Endocrinol Metab* (2020) 105(3):dgz113. doi: 10.1210/clinem/dgz113
67. Cho SJ, Suh CH, Baek JH, Chung SR, Choi YJ, Chung K-W, et al. Active Surveillance for Small Papillary Thyroid Cancer: A Systematic Review and

Meta-Analysis. *Thyroid: Off J Am Thyroid Assoc* (2019) 29:1399–408. doi: 10.1089/thy.2019.0159
68. Saravana-Bawan B, Bajwa A, Paterson J, McMullen T. Active surveillance of low-risk papillary thyroid cancer: A meta-analysis. *Surgery* (2020) 167:46–55. doi: 10.1016/j.surg.2019.03.040
69. Kim HI, Jang HW, Ahn HS, Ahn S, Park SY, Oh YL, et al. High Serum TSH Level Is Associated With Progression of Papillary Thyroid Microcarcinoma During Active Surveillance. *J Clin Endocrinol Metab* (2018) 103:446–51. doi: 10.1210/jc.2017-01775
70. Hirokawa M, Kudo T, Ota H, Suzuki A, Miyauchi A. Pathological characteristics of low-risk papillary thyroid microcarcinoma with progression during active surveillance. *Endocr J* (2016) 63:805–10. doi: 10.1507/endocrj.EJ16-0097
71. Kwon H, Oh H-S, Kim M, Park S, Jeon MJ, Kim WG, et al. Active Surveillance for Patients With Papillary Thyroid Microcarcinoma: A Single Center's Experience in Korea. *J Clin Endocrinol Metab* (2017) 102:1917–25. doi: 10.1210/jc.2016-4026
72. Sugitani I, Fujimoto Y, Yamada K. Association between serum thyrotropin concentration and growth of asymptomatic papillary thyroid microcarcinoma. *World J Surg* (2014) 38:673–8. doi: 10.1007/s00268-013-2335-8
73. Miyauchi A. Clinical Trials of Active Surveillance of Papillary Microcarcinoma of the Thyroid. *World J Surg* (2016) 40:516–22. doi: 10.1007/s00268-015-3392-y
74. Brito JP, Ito Y, Miyauchi A, Tuttle RM. A Clinical Framework to Facilitate Risk Stratification When Considering an Active Surveillance Alternative to Immediate Biopsy and Surgery in Papillary Microcarcinoma. *Thyroid: Off J Am Thyroid Assoc* (2016) 26:144–9. doi: 10.1089/thy.2015.0178
75. Moon JH, Kim JH, Lee EK, Lee KE, Kong SH, Kim YK, et al. Study Protocol of Multicenter Prospective Cohort Study of Active Surveillance on Papillary Thyroid Microcarcinoma (MAeSTro). *Endocrinol Metab (Seoul Korea)* (2018) 33:278–86. doi: 10.3803/EnM.2018.33.2.278
76. Sawka AM, Ghai S, Tomlinson G, Rotstein L, Gilbert R, Gullane P, et al. A protocol for a Canadian prospective observational study of decision-making on active surveillance or surgery for low-risk papillary thyroid cancer. *BMJ Open* (2018) 8:e020298. doi: 10.1136/bmjopen-2017-020298
77. Sawka AM, Ghai S, Yoannidis T, Rotstein L, Gullane PJ, Gilbert RW, et al. A Prospective Mixed-Methods Study of Decision-Making on Surgery or Active Surveillance for Low-Risk Papillary Thyroid Cancer. *Thyroid: Off J Am Thyroid Assoc* (2020) 30(7):999–1007. doi: 10.1089/thy.2019.0592
78. Rodrigues AC, Penna G, Rodrigues E, Castro P, Sobrinho-Simões M, Soares P. The Genetics of Papillary Microcarcinomas of the Thyroid: Diagnostic and Prognostic Implications. *Curr Genomics* (2017) 18:244–54. doi: 10.2174/1389202918666170105094459
79. Park YJ, Kim YA, Lee YJ, Kim SH, Park SY, Kim KW, et al. Papillary microcarcinoma in comparison with larger papillary thyroid carcinoma in BRAF(V600E) mutation, clinicopathological features, and immunohistochemical findings. *Head Neck* (2010) 32:38–45. doi: 10.1002/hed.21142
80. Song YS, Kang B-H, Lee S, Yoo S-K, Choi YS, Park J, et al. Genomic and Transcriptomic Characteristics According to Size of Papillary Thyroid Microcarcinoma. *Cancers* (2020) 12(5):1345. doi: 10.3390/cancers12051345
81. Kim KJ, Kim SG, Tan J, Shen X, Viola D, Elisei R, et al. BRAF V600E status may facilitate decision-making on active surveillance of low-risk papillary thyroid microcarcinoma. *Eur J Cancer (Oxford England: 1990)* (2020) 124:161–9. doi: 10.1016/j.ejca.2019.10.017
82. Chen Y, Sadow PM, Suh H, Lee KE, Choi JY, Suh YJ, et al. BRAF(V600E) Is Correlated with Recurrence of Papillary Thyroid Microcarcinoma: A Systematic Review, Multi-Institutional Primary Data Analysis, and Meta-Analysis. *Thyroid: Off J Am Thyroid Assoc* (2016) 26:248–55. doi: 10.1089/thy.2015.0391
83. Yabuta T, Matsuse M, Hirokawa M, Yamashita S, Mitsutake N, Miyauchi A. TERT Promoter Mutations Were Not Found in Papillary Thyroid Microcarcinomas That Showed Disease Progression on Active Surveillance. *Thyroid: Off J Am Thyroid Assoc* (2017) 27:1206–7. doi: 10.1089/thy.2016.0645
84. Kim SY, Kim T, Kim K, Bae JS, Kim JS, Jung CK. Highly prevalent BRAF V600E and low-frequency TERT promoter mutations underlie papillary thyroid carcinoma in Koreans. *J Pathol Trans Med* (2020) 54:310–7. doi: 10.4132/jptm.2020.05.12
85. Rusinek D, Pfeifer A, Krajewska J, Oczko-Wojciechowska M, Handkiewicz-Junak D, Pawlaczek A, et al. Coexistence of TERT Promoter Mutations and the BRAF V600E Alteration and Its Impact on Histopathological Features of Papillary Thyroid Carcinoma in a Selected Series of Polish Patients. *Int J Mol Sci* (2018) 19(9):2647. doi: 10.3390/ijms19092647
86. de Biase D, Gandolfi G, Ragazzi M, Eszlinger M, Sancisi V, Gugnoni M, et al. TERT Promoter Mutations in Papillary Thyroid Microcarcinomas. *Thyroid: Off J Am Thyroid Assoc* (2015) 25:1013–9. doi: 10.1089/thy.2015.0101
87. Rogers WA, Craig WL, Entwistle VA. Ethical issues raised by thyroid cancer overdiagnosis: A matter for public health? *Bioethics* (2017) 31:590–8. doi: 10.1111/bioe.12383
88. Ito Y, Miyauchi A, Kudo T, Oda H, Yamamoto M, Sasai H, et al. Trends in the Implementation of Active Surveillance for Low-Risk Papillary Thyroid Microcarcinomas at Kuma Hospital: Gradual Increase and Heterogeneity in the Acceptance of This New Management Option. *Thyroid: Off J Am Thyroid Assoc* (2018) 28:488–95. doi: 10.1089/thy.2017.0448
89. Nasef HO, Nixon IJ, Wreesmann VB. Optimization of the risk-benefit ratio of differentiated thyroid cancer treatment. *Eur J Surg Oncol : J Eur Soc Surg Oncol Br Assoc Surg Oncol* (2018) 44:276–85. doi: 10.1016/j.ejso.2018.01.077
90. Wallner LP, Reyes-Gastelum D, Hamilton AS, Ward KC, Hawley ST, Haymart MR. Patient-Perceived Lack of Choice in Receipt of Radioactive Iodine for Treatment of Differentiated Thyroid Cancer. *J Clin Oncol : Off J Am Soc Clin Oncol* (2019) 37:2152–61. doi: 10.1200/JCO.18.02228
91. Brito JP, Moon JH, Zeuren R, Kong SH, Kim YG, Iñiguez-Ariza NM, et al. Thyroid Cancer Treatment Choice: A Pilot Study of a Tool to Facilitate Conversations with Patients with Papillary Microcarcinomas Considering Treatment Options. *Thyroid: Off J Am Thyroid Assoc* (2018) 28:1325–31. doi: 10.1089/thy.2018.0105
92. Davies L, Hendrickson CD, Hanson GS. Experience of US Patients Who Self-identify as Having an Overdiagnosed Thyroid Cancer: A Qualitative Analysis. *JAMA Otolaryngol – Head Neck Surg* (2017) 143:663–9. doi: 10.1001/jamaoto.2016.4749
93. Davies L, Roman BR, Fukushima M, Ito Y, Miyauchi A. Patient Experience of Thyroid Cancer Active Surveillance in Japan. *JAMA Otolaryngol – Head Neck Surg* (2019) 145:363–70. doi: 10.1001/jamaoto.2018.4131
94. Dixon PR, Tomlinson G, Pasternak JD, Mete O, Bell CM, Sawka AM, et al. The Role of Disease Label in Patient Perceptions and Treatment Decisions in the Setting of Low-Risk Malignant Neoplasms. *JAMA Oncol* (2019) 5:817–23. doi: 10.1001/jamaoncol.2019.0054
95. Nickel B, Barratt A, McGeechan K, Brito JP, Moynihan R, Howard K, et al. Effect of a Change in Papillary Thyroid Cancer Terminology on Anxiety Levels and Treatment Preferences: A Randomized Crossover Trial. *JAMA Otolaryngol – Head Neck Surg* (2018) 144:867–74. doi: 10.1001/jamaoto.2018.1272
96. Nickel B, Howard K, Brito JP, Barratt A, Moynihan R, McCaffery K. Association of Preferences for Papillary Thyroid Cancer Treatment With Disease Terminology: A Discrete Choice Experiment. *JAMA Otolaryngol – Head Neck Surg* (2018) 144:887–96. doi: 10.1001/jamaoto.2018.1694
97. Kong SH, Ryu J, Kim MJ, Cho SW, Song YS, Yi KH, et al. Longitudinal Assessment of Quality of Life According to Treatment Options in Low-Risk Papillary Thyroid Microcarcinoma Patients: Active Surveillance or Immediate Surgery (Interim Analysis of MAeSTro). *Thyroid: Off J Am Thyroid Assoc* (2019) 29:1089–96. doi: 10.1089/thy.2018.0624
98. Oda H, Miyauchi A, Ito Y, Yoshioka K, Nakayama A, Sasai H, et al. Incidences of Unfavorable Events in the Management of Low-Risk Papillary Microcarcinoma of the Thyroid by Active Surveillance Versus Immediate Surgery. *Thyroid: Off J Am Thyroid Assoc* (2016) 26:150–5. doi: 10.1089/thy.2015.0313
99. Smulever A, Pitoia F. High rate incidence of post-surgical adverse events in patients with low-risk papillary thyroid cancer who did not accept active surveillance. *Endocrine* (2020) 69(3):587–95. doi: 10.1007/s12020-020-02310-8
100. Büttner M, Hinz A, Singer S, Musholt T. Quality of Life of Patients More Than 1 Year After Surgery for Thyroid Cancer. *Hormones (Athens Greece)* (2020) 19(2):233–43. doi: 10.1007/s42000-020-00186-x
101. Jeon MJ, Lee Y-M, Sung T-Y, Han M, Shin Y-W, Kim WG, et al. Quality of Life in Patients with Papillary Thyroid Microcarcinoma Managed by Active

Surveillance or Lobectomy: A Cross-Sectional Study. *Thyroid: Off J Am Thyroid Assoc* (2019) 29:956–62. doi: 10.1089/thy.2018.0711
102. Ullmann TM, Gray KD, Limberg J, Stefanova D, Moore MD, Buicko J, et al. Insurance Status Is Associated with Extent of Treatment for Patients with Papillary Thyroid Carcinoma. *Thyroid: Off J Am Thyroid Assoc* (2019) 29:1784–91. doi: 10.1089/thy.2019.0245
103. Morris LGT, Sikora AG, Tosteson TD, Davies L. The increasing incidence of thyroid cancer: the influence of access to care. *Thyroid: Off J Am Thyroid Assoc* (2013) 23:885–91. doi: 10.1089/thy.2013.0045
104. Jensen C, Saucke M, Francis D, Voils C, Pitt S. From Overdiagnosis to Overtreatment of Low-Risk Thyroid Cancer: A Thematic Analysis of Attitudes and Beliefs of Endocrinologists, Surgeons, and Patients. *Thyroid: Off J Am Thyroid Assoc* (2020) 30(5):696–703. doi: 10.1089/thy.2019.0587
105. Lubitz C, Kong C, McMahon P, Daniels GH, Chen Y, Economopoulos K, et al. Annual Financial Impact of Well-Differentiated Thyroid Cancer Care in the United States. *Cancer* (2014) 120 (9):1345–52. doi: 10.1002/cncr.28562
106. Lamartina L, Handkiewicz-Junak D. Follow-up of low risk thyroid cancer patients: can we stop follow-up after 5 years of complete remission? *Eur J Endocrinol* (2020) 182:D1–D16. doi: 10.1530/EJE-19-0960
107. Wong CKH, Liu X, Lang BHH. Cost-effectiveness of fine-needle aspiration cytology (FNAC) and watchful observation for incidental thyroid nodules. *J Endocrinol Invest* (2020). doi: 10.1007/s40618-020-01254-0
108. Oda H, Miyauchi A, Ito Y, Sasai H, Masuoka H, Yabuta T, et al. Comparison of the costs of active surveillance and immediate surgery in the management of low-risk papillary microcarcinoma of the thyroid. *Endocr J* (2017) 64:59–64. doi: 10.1507/endocrj.EJ16-0381
109. Lang BH-H, Wong CKH. A cost-effectiveness comparison between early surgery and non-surgical approach for incidental papillary thyroid microcarcinoma. *Eur J Endocrinol* (2015) 173:367–75. doi: 10.1530/EJE-15-0454
110. Venkatesh S, Pasternak JD, Beninato T, Drake FT, Kluijfhout WP, Liu C, et al. Cost-effectiveness of active surveillance versus hemithyroidectomy for micropapillary thyroid cancer. *Surgery* (2017) 161:116–26. doi: 10.1016/j.surg.2016.06.076
111. Lin JF, Jonker PKC, Cunich M, Sidhu SB, Delbridge LW, Glover AR, et al. Surgery alone for papillary thyroid microcarcinoma is less costly and more effective than long term active surveillance. *Surgery* (2020) 167:110–6. doi: 10.1016/j.surg.2019.05.078

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 08 October 2020
doi: 10.3389/fendo.2020.553577

# Management of Clinically Solitary Papillary Thyroid Carcinoma Patients According to Risk-Scoring Model for Contralateral Occult Carcinoma

*Jia-Wei Feng[1], Jing Ye[1], Wan-Xiao Wu[1], Hua Pan[1], An-Cheng Qin[2], Yong Jiang[1]* and Bao-Qiang Wu[3]**

*[1] Department of Thyroid Surgery, The Third Affiliated Hospital of Soochow University, Changzhou First People's Hospital, Changzhou, China, [2] Department of General Surgery, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Suzhou, China, [3] Department of General Surgery, The Second People's Hospital of Changzhou affiliated to Nanjing Medical University, Changzhou, China*

OPEN ACCESS

**Edited by:**
*Christoph Reiners, University Hospital Würzburg, Germany*

**Reviewed by:**
*Francesco Frasca, University of Catania, Italy*
*Silvia Martina Ferrari, University of Pisa, Italy*

***Correspondence:**
*Yong Jiang*
*yjiang8888@hotmail.com*
*Bao-Qiang Wu*
*gif55171@163.com*

**Specialty section:**
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

**Received:** *19 April 2020*
**Accepted:** *17 September 2020*
**Published:** *08 October 2020*

**Citation:**
*Feng J-W, Ye J, Wu W-X, Pan H, Qin A-C, Jiang Y and Wu B-Q (2020) Management of Clinically Solitary Papillary Thyroid Carcinoma Patients According to Risk-Scoring Model for Contralateral Occult Carcinoma. Front. Endocrinol. 11:553577. doi: 10.3389/fendo.2020.553577*

**Objective:** The aim of this study was to investigate risk factors of occult carcinoma in clinically solitary papillary thyroid carcinoma (PTC) patients, and to put emphasis on the predictive value of risk-scoring model to determine the optimal scope of surgery

**Methods:** A total of 573 clinically solitary PTC patients who underwent total thyroidectomy (TT) from two hospitals were retrospectively analyzed. Clinicopathological features were collected, univariate and multivariate analyses were performed to determine risk factors of occult carcinoma. The Cox proportional hazards model was used to analyze the risk factors of recurrence. A scoring model was constructed according to independent risk factors of contralateral occult carcinoma.

**Results:** 19.2% of clinically solitary PTC patients had occult carcinoma, among which 3.7% patients had ipsilateral occult carcinoma and 15.5% patients had contralateral occult carcinoma. Factors such as male, the presence of benign nodule, and vascular invasion increase the risk of ipsilateral occult carcinoma. Tumor size >1 cm, the presence of benign nodule, extrathyroidal extension, central lymph node metastasis, lateral lymph node metastasis are independent predictors of contralateral occult carcinoma. Contralateral occult carcinoma is the independent predictor of recurrence. A 10-point risk-scoring model was established to predict the contralateral occult carcinoma in clinically solitary PTC patients.

**Conclusion:** Lobectomy is sufficient for clinically solitary PTC patients with risk factors of ipsilateral occult carcinoma. For clinically solitary PTC patients with score ≥4, careful preoperative evaluations are required to rule out the contralateral occult carcinoma. Even if contralateral occult carcinoma is not detected preoperatively, TT is recommended for high-risk patients.

**Keywords: papillary thyroid microcarcinoma, contralateral occult carcinoma, ipsilateral occult carcinoma, recurrence-free survival, surgery**

## INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common endocrine malignant tumor worldwide, accounting for approximately 80.0% of thyroid malignant tumors (1, 2). Although the incidence of PTC has increased rapidly in incidence, understanding of PTC has become more and more thorough from the molecular, diagnostic, and prognostic perspectives. According to the 2004 World Health Organization "Thyroid and Parathyroid Diseases and Genetic Classification", in addition to the most common classic PTC, there are 15 subtypes of PTC, among which highly aggressive PTC variants, such as diffuse sclerosing, tall-cell, insular, and poorly differentiated subtypes, exhibit heterogeneous clinical behavior and a wide range of mortality risk (3). Fine needle aspiration (FNA) of thyroid nodules can detect different gene mutations and other molecular changes in PTC, and the use of molecular pathways has permitted the development of new targeted therapies for aggressive PTC (4).

Despite the progress has been made in understanding the basic biological characteristics of PTC, the optimal scope of surgery, lobectomy vs total thyroidectomy (TT), is still controversial. As reported, PTC frequently occurs as multifocal lesions, with the prevalence of multifocality ranging from 20.0 to 36.1% (5–7). For tumors preoperatively detected in the bilateral lobes, there is no controversial to perform TT. Considering the possibility of recurrent or persistent carcinoma in the remnant contralateral lobe, TT seems to be applicable for tumors confined to the unilateral lobe. The rate of contralateral occult PTC discovered by TT was reported to range from 10 to 30% (8–11). Considering the high incidence of postoperative complications, the routine use of TT is not recommended for all patients with unilateral PTC. However, multifocal PTCs were reported to be associated with poor outcome, and increased risk of recurrence (7, 12, 13). High resolution of ultrasonography (US), which could detect foci as small as 2–3 mm, is currently used in detecting PTC and determining the scope of surgery (14). However, smaller tumors remain undetected. In addition, the ability of US to detect small malignant tumors would be significantly reduced when patients had diffuse thyroid disease (15).

Therefore, identifying risk factors of occult carcinoma in the thyroid lobe may help surgeons determine the optimal scope of surgery. By using a large series of patients who underwent initially TT for the treatment of a single PTC confined to only the unilateral lobe, we aimed to identify risk factors of occult carcinoma. In addition, we investigated the effects of occult carcinoma on clinical outcomes of patients. Different from previous studies, we established a model based on the risk factors of occult carcinoma. According to this risk-scoring model, we can predict high-risk populations of occult carcinoma among solitary PTC patients for the avoidance of unnecessary TT, and provide individualized treatment for high-risk populations of occult carcinoma.

**Abbreviations:** PTC, papillary thyroid carcinoma; TT, total thyroidectomy; US, ultrasonography; FNA, fine-needle aspiration; CT, computed tomography; CND, central neck dissection; LND, lateral neck dissection; pCND, prophylactic central neck dissection; CLNM, central lymph node metastasis; cN0, clinically lymph node-negative; PTMC, papillary thyroid microcarcinoma; ETE, extrathyroidal extension; RFS, recurrence-free survival; LT4, levothyroxine; TSH, thyroid-stimulating hormone; SD, standard deviations; ROC, receiver operating characteristic; ATA, American Thyroid Association.

## MATERIALS AND METHODS

### Patients

This multi-center retrospective cohort study consisted of patients from Changzhou First People's Hospital and Suzhou Municipal Hospital between January 2011 and January 2018. These patients underwent initially TT for the treatment of a single PTC confined to only the unilateral lobe, without other suspicious carcinoma lesions in the contralateral lobe by preoperative image examinations or FNA. The Institutional Review Board of Changzhou First People's Hospital and Suzhou Municipal Hospital approved this retrospective study. All participants gave written informed consent for their clinical records to be used in this study. Patients were excluded from the study if they have any of following factors: (1) patients with preoperative clinical evidence of multiple PTCs or other pathologic types of thyroid malignancies; (2) patients with the single PTC had another suspicious lesion, but FNA was not performed for the suspicious lesion; (3) non-PTCs (medullary/follicular/anaplastic) or other subtypes than classic PTC (such as mixed PTC and so on); (4) patients did not undergo the TT; (5) patients had another malignancy before thyroidectomy; (6) patients with diffuse thyroid disease; (7) reoperation; (8) distant metastasis at diagnosis on pathological or clinical analysis; (9) history of neck radiation or familial cancer; (10) incomplete clinical data or missing follow-up. Finally, a total of 573 patients were enrolled in this study.

### Surgical Procedures

We used the US, computed tomography (CT), or FNA to evaluate primary lesions and lymph nodes in the neck preoperatively. All patients underwent TT. TT was defined as the removal of two lobes, the isthmus, and the pyramidal lobe. For patients with clinically positive central lymph node metastasis (CLNM), therapeutic central neck dissection (CND) would be performed. All clinically lymph node-negative (cN0) PTC patients underwent prophylactic central neck dissection (pCND). CND plus therapeutic ipsilateral lateral neck dissection (LND) were performed for patients with clinically positive or intraoperative suspected lateral lymph node metastasis (LLNM). The central compartment refers to level VI. CND and pCND included the removal of prelaryngeal, pretracheal, and bilateral paratracheal lymph nodes (16). LND was performed in the usual fashion from at least level II to level V, sparing the internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle (17). According to neck levels, all lymph nodes specimens were separated by the surgeon and were sent to the department of pathology for paraffin fixation and histological analysis.

## Histopathologic Examination of Surgical Specimens

Two or more experienced pathologists reviewed and cross-checked all pathology specimens microscopically. Contralateral occult carcinoma, the tumor lesion detected by pathology postoperatively in the contralateral lobe rather than detected by preoperative examinations. Similarly, ipsilateral occult carcinoma was the tumor lesion detected by pathology postoperatively in the ipsilateral lobe rather than detected by preoperative examinations. Two or more PTC foci within the thyroid was defined as multifocality. Two or more PTC foci in a single lobe were ipsilateral multifocality, while two or more PTC foci in both lobes were bilateral multifocality. Papillary thyroid microcarcinoma (PTMC) was defined as PTC ≤1 cm in its maximum diameter. Extrathyroidal extension (ETE) was defined as the primary tumor extending through the thyroid capsule to perithyroidal soft tissue, or involving strap muscles, or extending to surrounding structures (18). PTC was subdivided into the following three groups according to the position: upper pole (upper part of the high plane of the isthmus), middle pole (parallel to the isthmus), and lower pole (lower part of the low plane of the isthmus). The location of the tumor was determined by the largest dominant lesion when the patient had multifocal lesions. When the dominant lesion occupied 2 adjacent parts, the location of the tumor was determined by the portion containing more than two-thirds of the tumor volume. Recurrence was defined as the any new lesions detected in cervical lymph nodes, or other organs on cytology from aspiration biopsy. Recurrence-free survival (RFS) was used to evaluate the outcomes. RFS was the duration started from the surgery to recurrence.

## Postoperative Management and Follow-Up

Postoperative suppressive levothyroxine (LT4) treatment was conventionally performed in all patients. Thyroid-stimulating hormone (TSH) suppression therapy (serum TSH level below 0.5 mIU/L) with LT4 with or without radioactive iodine (RAI) ablation was administered to patients who underwent TT. After the initial surgery, physical examinations, US of the neck, and serum thyroid function (free thyroxin, TSH, thyroglobulin and anti-thyroglobulin antibodies) were performed for all patients every 6 months for a period of 2 years, and thereafter once a year. The criteria for remission was defined as (1) no evidence of tumor recurrence in clinical or radiologic examination, and (2) serum thyroglobulin levels of <2 ng/ml during TSH stimulation and <1 ng/ml during TSH suppression in the absence of anti-thyroglobulin antibodies. Disease recurrence, which included the local, regional, and distant recurrence, was defined as new evidence of pathologically proven recurrence in patients who initially met the criteria of remission. After the radiographic or biochemical examinations, histological examination of new lesion would be performed to verify whether the lesion was the recurrent PTC.

## Statistical Analyses

All statistical analyses were performed using the SPSS v 25.0 software (Chicago, IL, USA). The continuous variables were expressed as means ± standard deviations (SD). Univariate analysis for the comparison between patient groups was used Pearson's chi-square test or Fisher's exact test. Variables with a $P$ <0.05 in the univariate analysis were included in the multivariate analysis, which were performed logistic regression analysis to assess risk factors of contralateral/ipsilateral occult carcinoma. The potential relationship between clinicopathological variables and recurrence was used the Cox proportional hazards model to analyze. A risk-scoring model was constructed to calculate the probability of contralateral occult carcinoma on the basis of results in the multivariate analysis. The independent risk factors were selected as scoring items. According to the beta coefficient obtained from the logistic regression model, the score of each risk factor was weighted. To make the scoring model simple, all the beta coefficient divided the least one and then rounded to the nearest whole number. The total score for each patient represented the sum of scores for each risk factor. Receiver operating characteristic (ROC) curve was used to evaluate the predictive performance of the scoring model and find an appropriate cut-off point.

# RESULTS

## Base Clinicopathological Characteristics of Patients

The baseline clinicopathological characteristics of patients are summarized in **Table 1**. Among the 573 PTC patients, there were 134 men and 439 women with the mean age of 44.7±12.3 years (range from 19 to 80 years). The mean BMI was 22.39±5.34 kg/$m^2$ (range from 11.03 to 39.06 kg/$m^2$), and 208 (36.3%) patients were overweight. The diameter of the tumors ranged from 0.10 to 6.00 cm with the mean diameter of 1.20±0.87 cm. Among 64 PTC patients who performed BRAF mutation analysis, 56 (87.5%) patients had BRAF mutation positivity. Histopathological examination of specimens showed that one hundred and six (18.5%) patients had benign thyroid nodules. Occult PTC foci were detected in the contralateral lobe in 89 (15.5%) patients, and in the ipsilateral lobe in 21 (3.7%) patients. The ETE and vascular invasion were detected in 84 (14.7%) and 28 (4.9%) patients, respectively. Tumor located in the upper portion of the thyroid gland was detected in 221 (38.6%) patients, and tumor located in the middle/lower lobe of thyroid was detected in 352 (61.4%) patients. CLNM only was present in 207 patients (36.1%), both CLNM and LLNM were present in 64 patients (11.2%), and LLNM only was present in 20 patients (3.5%). The mean number of removed and metastatic lymph nodes in the central compartment was 6.0±4.6 and 2.5±1.5, respectively. And the mean number of removed and metastatic lymph nodes in the lateral compartment was 18.3±11.5 and 5.0±4.8, respectively.

## Clinicopathological Factors Associated With Contralateral Occult Carcinoma

Among 89 patients with occult lesions in the contralateral gland, 31 patients had occult lesions in the upper portion of the thyroid

**TABLE 1** | Clinicopathological characteristics of 573 PTC patients.

| Clinicopathological characteristics | No. (%) |
|---|---|
| Sex | |
| Male | 134 (23.4%) |
| Female | 439 (76.6%) |
| Age (Y), Mean±SD (range) | 44.7 ± 12.3 (19–80) |
| ≥55 | 113 (19.7%) |
| <55 | 460 (80.3%) |
| BMI (kg/m$^2$), Mean±SD (range) | 22.39 ± 5.34 (11.03–39.06) |
| Normal | 365 (63.7%) |
| Overweight | 208 (36.3%) |
| Maximum tumor size (cm), Mean±SD (range) | 1.20 ± 0.87 (0.10–6.00) |
| ≤1 | 283 (49.4%) |
| >1 | 290 (50.6%) |
| BRAF mutation* | |
| Absence | 8 (12.5%) |
| Presence | 56 (87.5%) |
| With benign nodule | |
| Absence | 467 (81.5%) |
| Presence | 106 (18.5%) |
| Occult carcinoma | |
| Absence | 463 (80.8%) |
| Contralateral occult carcinoma | 89 (15.5%) |
| Ipsilateral occult carcinoma | 21 (3.7%) |
| ETE | |
| Absence | 489 (85.3%) |
| Presence | 84 (14.7%) |
| Vascular invasion | |
| Absence | 545 (95.1%) |
| Presence | 28 (4.9%) |
| Tumor location | |
| Upper | 221 (38.6%) |
| Middle/Lower | 352 (61.4%) |
| LNM | |
| Without LNM | 282 (49.2%) |
| CLNM only | 207 (36.1%) |
| LLNM only | 20 (3.5%) |
| CLNM and LLNM | 64 (11.2%) |
| No. of removed LNs in CC, Mean±SD (range) | 6.0 ± 4.6 (2–32) |
| No. of removed LNs in LC, Mean±SD (range) | 18.3 ± 11.5 (5–51) |
| No. of metastatic LNs in CC, Mean±SD (range) | 2.5 ± 1.5 (0–18) |
| No. of metastatic LNs in LC, Mean±SD (range) | 5.0 ± 4.8 (3–22) |
| Recurrence | 31 (5.4%) |
| LNs | 29 (5.1%) |
| Lung | 2 (0.3%) |

*PTC, papillary thyroid carcinoma; Y, year; SD, standard deviation; ETE, extrathyroidal extension; LNM, lymph node metastasis; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; LN, lymph node; CC, central compartment; LC, lateral compartment.*

**BRAF mutation analysis was started in 2017 and it was performed in 64 patients with PTC.*

glands, and 58 patients had occult lesions in the middle/lower lobe poles of the glands. The mean size of the contralateral occult lesion was 0.27±0.19 cm (range 0.10–0.35 cm). No contralateral occult lesions exhibited the ETE. In **Table 2**, contralateral occult carcinoma presented the significant association with tumor size, the presence of benign nodule, ETE, vascular invasion, CLNM, and LLNM by univariate analysis (all $P < 0.05$). All of these factors were included in the multivariate analysis and showed that tumor size >1 cm (OR: 2.280, 95% CI: 1.111–4.680, $P = 0.025$), the presence of benign nodule (OR: 7.361, 95% CI: 3.678–14.731, $P < 0.001$), ETE (OR: 15.324, 95% CI: 7.428–31.615, $P < 0.001$), CLNM (OR: 4.125, 95% CI: 1.914–8.891, $P < 0.001$), LLNM (OR: 6.983, 95% CI: 3.492–13.966, $P < 0.001$) remained independent predictors of contralateral occult carcinoma.

## Clinicopathological Factors Associated With Ipsilateral Occult Carcinoma

Of 21 patients with occult lesions in the ipsilateral gland, 6 patients had occult lesions in the upper portion of the thyroid glands, and 15 patients had occult lesions in the middle/lower lobe poles of the glands. The mean size of the ipsilateral occult lesion was 0.24±0.16 cm (range 0.10–0.31 cm). No ipsilateral occult lesions exhibited the ETE. As summarized in **Table 3**, univariate analysis revealed that male, the presence of benign nodule, ETE, and vascular invasion were significantly associated with the presence of ipsilateral occult carcinoma (all $P < 0.05$). All of these factors were included in the multivariate analysis and revealed that male (OR: 45.286, 95% CI: 4.819–425.574, $P = 0.001$), the presence of benign nodule (OR: 9.858, 95% CI: 2.120–45.842, $P = 0.004$), and vascular invasion (OR: 68.081, 95% CI: 7.440–662.304, $P < 0.001$) were independent predictive factors of ipsilateral occult carcinoma.

## Predictors of RFS

Postoperative follow-up ranged from 7 to 89 months (average follow-up period: 32 months). During follow-up, 31 (5.4%) patients developed recurrent disease, including 29 (5.1%) patients had cervical lymph nodes recurrence and 2 (0.3%) patients had lung recurrence.

Cox regression model in relation to RFS was conducted to determine variables which influenced recurrence. Our results showed tumor size, bilaterality, ETE, and CLNM were factors associated with recurrence (all $P < 0.05$). Multivariate analyses showed tumor size >1 cm (HR: 2.147, 95% CI: 1.005–4.585, $P = 0.048$), bilaterality (HR: 5.818, 95% CI: 2.196–15.415, $P < 0.001$), ETE (HR: 2.447, 95% CI: 1.033–5.793, $P = 0.042$), and CLNM (HR: 5.230, 95% CI: 1.818–15.046, $P = 0.002$) were independent risk predictors of recurrence, while other investigated variables had no significant influence on RFS (**Table 4**).

## Development of Risk-Scoring Model to Predict Contralateral Occult Carcinoma

Considering that the bilaterality was the independent risk predictor of recurrence, we established the risk-scoring model to predict the contralateral occult carcinoma in solitary PTC patients. As shown in **Table 5**, based on the beta coefficient of the five independent risk factors (tumor size, the presence of benign nodule, ETE, CLNM, and LLNM) identified in the multivariate analysis of contralateral occult carcinoma, a 10-point risk-scoring model was constructed.

According to the scoring model, the percentage of positive contralateral occult carcinoma ranged from 1.3 to 100.0% in order of total score in PTC patients (**Table 6**). A ROC curve of the risk-scoring model for contralateral occult carcinoma was plotted, and the area under the curve of the model for the prediction of contralateral occult carcinoma was 0.910 (95% CI: 0.872–0.948, $P < 0.001$), indicating that the discriminative power of this model is acceptable (**Figure 1**). Moreover, a total score of

**TABLE 2 |** Associations between clinicopathological characteristics and contralateral occult carcinoma in PTC patients.

| Variables | Contralateral occult | Solitary | *P* value | OR | 95% CI | *P* value |
|---|---|---|---|---|---|---|
| | N = 89 (16.1%) | N = 463 (83.9%) | | | | |
| Sex | | | | | | |
| Female | 22 (24.7%) | 95 (20.5%) | | | | |
| Male | 67 (75.3%) | 368 (79.5%) | 0.375 | | | |
| Age (Y) | | | | | | |
| ≥ 55 | 12 (13.5%) | 95 (20.5%) | | | | |
| < 55 | 77 (86.5%) | 368 (79.5%) | 0.124 | | | |
| BMI (kg/m$^2$) | | | | | | |
| Normal | 62 (69.7%) | 290 (62.6%) | | | | |
| Overweight | 27 (30.3%) | 173 (37.4%) | 0.206 | | | |
| Tumor size (cm) | | | | | | |
| ≤ 1 | 22 (24.7%) | 253 (54.6%) | | 1 | | |
| > 1 | 67 (75.3%) | 210 (45.4%) | <0.001 | 2.280 | 1.111–4.680 | 0.025 |
| BRAF mutation* | | | | | | |
| Absence | 1 (7.1%) | 6 (12.8%) | | | | |
| Presence | 13 (92.9%) | 41 (87.2%) | 0.919 | | | |
| With benign nodule | | | | | | |
| Absence | 44 (49.4%) | 409 (88.3%) | | 1 | | |
| Presence | 45 (50.6%) | 54 (11.7%) | <0.001 | 7.361 | 3.678–14.731 | <0.001 |
| ETE | | | | | | |
| Absence | 41 (46.1%) | 440 (95.0%) | | 1 | | |
| Presence | 48 (53.9%) | 23 (5.0%) | <0.001 | 15.324 | 7.428–31.615 | <0.001 |
| Vascular invasion | | | | | | |
| Absence | 80 (89.9%) | 459 (99.1%) | | 1 | | |
| Presence | 9 (10.1%) | 4 (0.9%) | <0.001 | 1.026 | 0.224–4.708 | 0.974 |
| Tumor location | | | | | | |
| Upper | 39 (43.8%) | 172 (37.1%) | | | | |
| Middle/Lower | 50 (56.2%) | 291 (62.9%) | 0.236 | | | |
| CLNM | | | | | | |
| Absence | 15 (16.9%) | 277 (59.8%) | | 1 | | |
| Presence | 74 (83.1%) | 186 (40.2%) | <0.001 | 4.125 | 1.914–8.891 | <0.001 |
| LLNM | | | | | | |
| Absence | 45 (50.6%) | 427 (92.9%) | | 1 | | |
| Presence | 44 (49.4%) | 36 (7.8%) | <0.001 | 6.983 | 3.492–13.966 | <0.001 |

*PTC, papillary thyroid carcinoma; Y, year; BMI, body mass index; ETE, extrathyroidal extension; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; OR, Odds ratio; 95% CI, 95% confidence interval.*

**BRAF mutation analysis was started in 2017 and it was performed in 61 PTC patients in this table.*

3.5 with the highest Youden's J value (0.717) was selected as the appropriate cut-off value for the model. Patients with a total score between 0 and 3 had the low risk of contralateral occult carcinoma, while patients with a total score ranging from 4 to 9 had the high risk of contralateral occult carcinoma.

## DISCUSSION

Continued attention has been paid to PTC given its increasing incidence, which is reaching epidemic proportions. The treatment of PTC, especially PTMC, remains the controversial topic. According to the latest American Thyroid Association (ATA) guidelines, TT is recommended for patients with tumor size >4cm, gross maximal ETE (T4), cervical lymph node metastasis, or distant metastasis. For preoperatively detected bilateral PTMC patients, TT is generally accepted, while for unilateral PTMC patients without ETE or cervical lymph node metastasis, lobectomy may be sufficient. In addition, considering that PTMC behaves more like a benign lesion, some scholars have proposed less aggressive strategies, such as "watch-and-wait" rather than surgery (19). However, some PTMCs may be occult and accompanied by aggressive behavior, which may lead to the local recurrence and cervical lymph node metastasis (8). In this study, we investigated the association between clinicopathological characteristics and occult carcinoma in order to identify solitary PTC patients with high risk of occult carcinoma, who would clearly benefit from a more extensive treatment.

In our study, we used the entire thyroid to determine the prevalence and distribution pattern of occult carcinoma in 573 consecutive patients with isolated nodule detected by preoperative US. Different from previous studies which defined "occult carcinoma" as the undetected carcinoma in the contralateral lobe when TT was performed in patients with preoperative unilateral PTC (20), we divided the occult carcinoma into contralateral and ipsilateral occult carcinoma. Our study found that 19.2% of clinically solitary PTC patients had occult carcinoma, among which 3.7% patients had ipsilateral occult carcinoma and 15.5% patients had contralateral occult carcinoma. The incidence of contralateral occult cancer in this study is consistent with the 10 to 30% reported in previous studies (8–11). Considering serious complications of TT, such as

**TABLE 3 |** Associations between clinicopathological characteristics and ipsilateral occult carcinoma in PTC patients.

| Variables | Ipsilateral occult | Solitary | *P* value | OR | 95% CI | *P* value |
|---|---|---|---|---|---|---|
| | N = 21 (4.3%) | N = 463 (95.7%) | | | | |
| Sex | | | | | | |
| Female | 4 (19.0%) | 368 (79.5%) | | 1 | | |
| Male | 17 (81.0%) | 95 (20.5%) | <0.001 | 45.286 | 4.819–425.574 | 0.001 |
| Age (Y) | | | | | | |
| ≥ 55 | 6 (28.6%) | 95 (20.5%) | | | | |
| < 55 | 15 (71.4%) | 368 (79.5%) | 0.539 | | | |
| BMI (kg/m$^2$) | | | | | | |
| Normal | 13 (61.9%) | 290 (62.6%) | | | | |
| Overweight | 8 (38.1%) | 173 (37.4%) | 0.946 | | | |
| Tumor size (cm) | | | | | | |
| ≤ 1 | 8 (38.1%) | 253 (54.6%) | | | | |
| > 1 | 13 (61.9%) | 210 (45.4%) | 0.137 | | | |
| BRAF mutation* | | | | | | |
| Absence | 1 (33.3%) | 6 (12.8%) | | | | |
| Presence | 2 (66.7%) | 41 (87.2%) | 0.378 | | | |
| With benign nodule | | | | | | |
| Absence | 14 (66.7%) | 409 (88.3%) | | 1 | | |
| Presence | 7 (33.3%) | 54 (11.7%) | 0.010 | 9.858 | 2.120–45.842 | 0.004 |
| ETE | | | | | | |
| Absence | 8 (38.1%) | 440 (95.0%) | | 1 | | |
| Presence | 13 (61.9%) | 23 (5.0%) | <0.001 | 2.152 | 0.139–33.219 | 0.583 |
| Vascular invasion | | | | | | |
| Absence | 6 (28.6%) | 459 (99.1%) | | 1 | | |
| Presence | 15 (71.4%) | 4 (0.9%) | <0.001 | 68.081 | 7.440–662.304 | <0.001 |
| Tumor location | | | | | | |
| Upper | 10 (47.6%) | 172 (37.1%) | | | | |
| Middle/Lower | 11 (52.4%) | 291 (62.9%) | 0.333 | | | |
| CLNM | | | | | | |
| Absence | 10 (47.6%) | 277 (59.8%) | | | | |
| Presence | 11 (52.4%) | 186 (40.2%) | 0.265 | | | |
| LLNM | | | | | | |
| Absence | 17 (81.0%) | 427 (92.2%) | | | | |
| Presence | 4 (19.0%) | 36 (7.8%) | 0.153 | | | |

*PTC, papillary thyroid carcinoma; Y, year; BMI, body mass index; ETE, extrathyroidal extension; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; OR, Odds ratio; 95% CI, 95% confidence interval.*

**BRAF mutation analysis was started in 2017 and it was performed in 50 PTC patients in this table.*

vocal cord paralysis and hypoparathyroidism, the 15.5% incidence of contralateral occult carcinoma cannot convince all patients with clinically solitary PTC to routinely undergo TT. Hence, we further examined any clinicopathological characteristics related to the presence of occult carcinoma, especially contralateral occult carcinoma, to help select high-risk patients with occult carcinoma.

In this study, factors such as male, the presence of benign nodule, and vascular invasion were independent predictors of ipsilateral occult carcinoma. As for contralateral occult carcinoma, tumor size >1 cm, the presence of benign nodule, ETE, CLNM, LLNM were independent predictors. Our results were consistent with previous studies regarding the risk factors of multifocality (21–23). To our surprise, the presence of benign nodule was the risk factor of both contralateral and ipsilateral occult carcinoma. This result may be due to the presence of occult small carcinoma obscured by benign nodules. Moreover, the accurate of US in detecting lesions with diameters less than 5 mm was only 53.8% (24), and 7.9 to 18% of the aspirates were classified as "indeterminate" by FNA, which carry the risk of malignancy (25, 26). Therefore, the presence of benign nodule in the lobe by preoperative evaluation should be regarded as the significant predictive factor of potential presence of the occult carcinoma in the both contralateral and ipsilateral lobe.

Due to the excellent prognosis of PTMC, some people hold the view that the treatment of PTMC should be different from PTC (19). We further analyzed risk factors of recurrence. In addition to the tumor size >1 cm, ETE, and CLNM, which previously confirmed to be associated with recurrence (27–30), we found bilaterality, that is, the occult carcinoma in the contralateral lobe, is also the independent predictor of recurrence. However, ipsilateral multifocality, that is, the occult carcinoma in the ipsilateral lobe, has no association with recurrence. This result was consistent with previous studies. For example, a recent study involving 2,211 Chinese PTC patients showed the 10-year disease-free survival rate of patients with bilateral PTC was much lower than that of those with unilateral-multifocal and solitary PTC (78.8 vs 85.7 and 89.3%, respectively; $P = 0.005$) (31). Moreover, a study of

**TABLE 4 |** Cox proportional hazards model demonstrating factors associated with recurrence-free survival in PTC patients.

| Variables | Univariate analyses | | | Multivariate analyses* | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* value | HR | 95% CI | *P* value |
| Sex | | | | | | |
| Male | 1 | | | | | |
| Female | 1.652 | 0.706–3.865 | 0.247 | | | |
| Age (Y) | | | | | | |
| < 55 | 1 | | | | | |
| ≥ 55 | 0.758 | 0.324–1.771 | 0.522 | | | |
| BMI (kg/m$^2$) | | | | | | |
| Normal | 1 | | | | | |
| Overweight | 1.841 | 0.875–3.872 | 0.108 | | | |
| Tumor size (cm) | | | | | | |
| ≤ 1 | 1 | | | 1 | | |
| > 1 | 2.621 | 1.094–6.280 | 0.031 | 2.147 | 1.005–4.585 | 0.048 |
| Multifocality | | | | | | |
| Solitary | 1 | | | 1 | | |
| Ipsilateral Multifocality | 1.262 | 0.639–2.490 | 0.503 | 1.398 | 0.339–5.757 | 0.643 |
| Bilaterality | 2.560 | 1.040–6.299 | 0.041 | 5.818 | 2.196–15.415 | <0.001 |
| ETE | | | | | | |
| Absence | 1 | | | 1 | | |
| Presence | 2.560 | 1.040–6.299 | 0.041 | 2.447 | 1.033–5.793 | 0.042 |
| Vascular invasion | | | | | | |
| Absence | 1 | | | | | |
| Presence | 1.390 | 0.560–3.450 | 0.477 | | | |
| Tumor location | | | | | | |
| Middle/Lower | 1 | | | | | |
| Upper | 1.322 | 0.659–2.650 | 0.432 | | | |
| CLNM | | | | | | |
| Absence | 1 | | | 1 | | |
| Presence | 5.047 | 1.712–14.877 | 0.003 | 5.230 | 1.818–15.046 | 0.002 |
| LLNM | | | | | | |
| Absence | 1 | | | | | |
| Presence | 1.091 | 0.529–2.250 | 0.814 | | | |

*PTC, papillary thyroid carcinoma; Y, year; BMI, body mass index; ETE, extrathyroidal extension; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; HR, Hazard ratio; 95% CI, 95% confidence interval.*

**The multivariate models were performed using a backward stepwise selection procedure. All clinically relevant variables with P < 0.05 in univariate results were used in the multivariate model.*

**TABLE 5 |** Development of a 10-point risk-scoring model to predict contralateral occult carcinoma in PTC patients.

| Variables | *P* value | Beta coefficient | Point |
|---|---|---|---|
| Tumor size (cm) | | | |
| ≤ 1 | | | |
| > 1 | 0.025 | 0.824 | 1.000 |
| With benign nodule | | | |
| Absence | | | |
| Presence | <0.001 | 1.996 | 2.000 |
| ETE | | | |
| Absence | | | |
| Presence | <0.001 | 2.729 | 3.000 |
| CLNM | | | |
| Absence | | | |
| Presence | <0.001 | 1.417 | 2.000 |
| LLNM | | | |
| Absence | | | |
| Presence | <0.001 | 1.944 | 2.000 |

*PTC, papillary thyroid carcinoma; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; ETE, extrathyroidal extension.*

**TABLE 6 |** Risk scores and percentage of contralateral occult carcinoma in PTC patients.

| Risk score | contralateral occult carcinoma (+) | contralateral occult carcinoma (–) | Total | Positive rate (%) |
|---|---|---|---|---|
| 0 | 2 | 147 | 149 | 1.3% |
| 1 | 4 | 101 | 105 | 3.8% |
| 2 | 1 | 74 | 75 | 1.3% |
| 3 | 8 | 88 | 96 | 8.3% |
| 4 | 8 | 18 | 26 | 30.8% |
| 5 | 14 | 22 | 36 | 38.9% |
| 6 | 25 | 11 | 36 | 69.4% |
| 7 | 13 | 0 | 13 | 100.0% |
| 8 | 7 | 2 | 9 | 77.8% |
| 9 | 7 | 0 | 7 | 100.0% |

*PTC, papillary thyroid microcarcinoma.*

2,095 patients with PTC who underwent TT found that multifocality rather than bilaterality was the independent predictor of disease recurrence or persistence (32). Therefore, conservative treatment, such as lobectomy, can be performed for clinically solitary PTC patients with risk factors of ipsilateral occult carcinoma.

In addition to showing contralateral occult carcinoma risk stratification data, we developed and validated a 10-point risk-

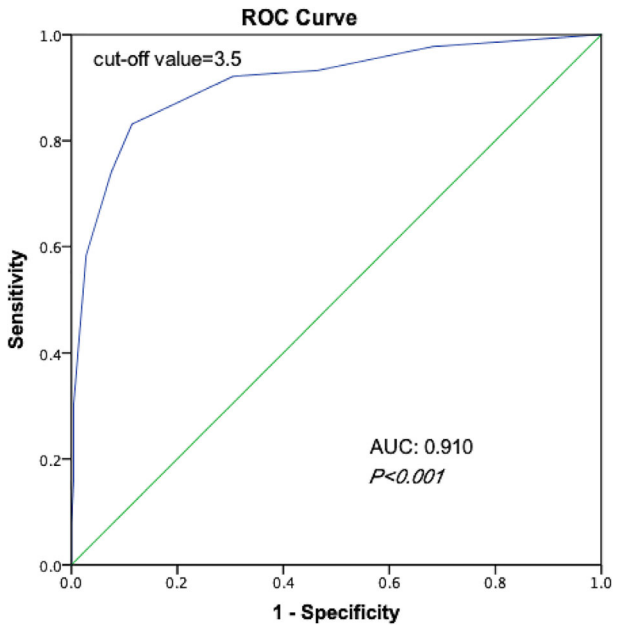


**FIGURE 1** | Receiver operating characteristic curves of the ability of risk-scoring model to predict the risk of contralateral occult carcinoma.

scoring model to predict the presence of contralateral occult carcinoma in clinically solitary PTC patients based on tumor size, the presence of benign nodule, ETE, CLNM, and LLNM in our study. Predictive models can not only understand the response probabilities of each predictor to other factors, but also quickly assess the response probabilities of individual subjects. According to the ROC curve, the area under the curve of the model for the prediction of contralateral occult carcinoma was 0.910 (95% CI: 0.872–0.948, $P < 0.001$), showing the high discrimination accuracy of the scoring model. The average incidence of contralateral occult carcinoma in PTC patients with score ≥4 (high risk) was significantly higher than that in patients with score ≤3 (low risk) (58.3 vs. 3.5%, $P < 0.001$). The risk scoring model is simple and effective, which could be implemented in clinical work. By identifying the high-risk groups in the relatively objective manner, it can provide the personalized treatment for these patients. For example, combined with preoperative image examinations, clinically solitary PTC patients with score ≥4 are recommended to undergo extensive treatment, such as TT, to improve the prognosis, while clinically solitary PTC patients with score ≤3 should undergo the lobectomy in consideration of high complication rates of TT

There are several potential limitations in our study, which expects to be extended upon in the further researches. First, our research was a retrospective study, which might have the selection bias. Compared with the prospective studies, retrospective studies tend to have more errors and biases. For instance, the data we provided were extracted from the document and were not captured in the actual conversation. The possibility of residual confounding variables of unmeasured factors could not be ruled out. Second, different surgeons were involved in performing TT and lymph node dissection. Postoperative results may be affected by surgeon-specific factors. Third, since LND is not generally recommended as a prophylactic procedure, there may be undetected LLNM. Moreover, the follow-up time was relatively short (average time: 32 months), which may lead to a low recurrence rate. Longer follow-up period may make the result more stable. Finally, more external validation, such as validation of the risk-scoring model in other institutions or other countries, is still necessary in the future.

In conclusion, our study found that male, the presence of benign nodule, and vascular invasion increase the risk of ipsilateral occult carcinoma in clinically solitary PTC patients. And tumor size >1 cm, the presence of benign nodule, ETE, CLNM, LLNM were independent predictors of contralateral occult carcinoma in clinically solitary PTC patients. Considering that bilaterality (occult carcinoma in the contralateral lobe) is the independent predictor of recurrence, we developed a 10-point risk-scoring model for contralateral occult carcinoma to better guide the treatment in clinically solitary PTC patients. For clinically solitary PTC patients with score ≥4, careful preoperative evaluations are required to exclude the contralateral occult carcinoma. Even if contralateral occult carcinoma is not detected preoperatively, TT is recommended for high-risk patients.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

This study has been approved by the Institutional Review Board of Changzhou First People's Hospital and Suzhou Municipal Hospital ethics committee, and has been performed according to the ethical standards laid down in the 1964 Declaration of Helsinki.

## AUTHOR CONTRIBUTIONS

A-CQ took charge of conceiving and designing the study. HP and W-XW were responsible for collecting the data and analyzing and interpreting the data. J-WF took charge of writing the manuscript. JY was responsible for providing critical revisions. B-QW participated in the revision of this manuscript and put forward important revisions. Approving the final version of the manuscript was in charge of YJ. All authors contributed to the article and approved the submitted version.

## ACKNOWLEDGMENTS

Lei Qin, the English language editor, was responsible for correcting language and grammar issues.

## REFERENCES


1. Seib CD, Sosa JA. Evolving Understanding of the Epidemiology of Thyroid Cancer. *Endocrinol Metab Clin North Am* (2019) 48(1):23–35. doi: 10.1016/j.ecl.2018.10.002
2. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. *Jama* (2017) 317 (13):1338–48. doi: 10.1001/jama.2017.2719
3. Ho AS, Luu M, Barrios L, Chen I, Melany M, Ali N, et al. Incidence and Mortality Risk Spectrum Across Aggressive Variants of Papillary Thyroid Carcinoma. *JAMA Oncol* (2020) 6(5):1–8. doi: 10.1001/jamaoncol.2019.6851
4. Ferrari SM, Fallahi P, Ruffilli I, Elia G, Ragusa F, Paparo SR, et al. Molecular testing in the diagnosis of differentiated thyroid carcinomas. *Gland Surg* (2018) 7(Suppl 1):S19–s29. doi: 10.21037/gs.2017.11.07
5. So YK, Kim MW, Son YI. Multifocality and bilaterality of papillary thyroid microcarcinoma. *Clin Exp Otorhinolaryngol* (2015) 8(2):174–8. doi: 10.3342/ceo.2015.8.2.174
6. Ng SC, Kuo SF, Chen ST, Hsueh C, Huang BY, Lin JD. Therapeutic Outcomes of Patients with Multifocal Papillary Thyroid Microcarcinomas and Larger Tumors. *Int J Endocrinol* (2017) 2017:4208178. doi: 10.1155/2017/4208178
7. Kuo SF, Lin SF, Chao TC, Hsueh C, Lin KJ, Lin JD. Prognosis of multifocal papillary thyroid carcinoma. *Int J Endocrinol* (2013) 2013:809382. doi: 10.1155/2013/809382
8. Chow SM, Law SC, Chan JK, Au SK, Yau S, Lau WH. Papillary microcarcinoma of the thyroid-Prognostic significance of lymph node metastasis and multifocality. *Cancer* (2003) 98(1):31–40. doi: 10.1002/cncr.11442
9. Hay ID, Hutchinson ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS, et al. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. *Surgery* (2008) 144(6):980–987; discussion 987-988. doi: 10.1016/j.surg.2008.08.035
10. Mercante G, Frasoldati A, Pedroni C, Formisano D, Renna L, Piana S, et al. Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. *Thyroid* (2009) 19(7):707–16. doi: 10.1089/thy.2008.0270
11. Schönberger J, Marienhagen J, Agha A, Rozeboom S, Bachmeier E, Schlitt H, et al. Papillary microcarcinoma and papillary cancer of the thyroid <or=1 cm: modified definition of the WHO and the therapeutic dilemma. *Nuklearmedizin* (2007) 46(4):115–20quiz N141–112. doi: 10.1160/nukmed-0059
12. Khan M, Syed AA, Khan AI, Hussain SR, Urooj N. Association of tumor size and focality with recurrence/persistence in papillary thyroid cancer patients treated with total thyroidectomy along with radioactive-iodine ablation and TSH suppression. *Updates Surg* (2018) 70(1):121–7. doi: 10.1007/s13304-017-0465-5
13. Choi WR, Roh JL, Gong G, Cho KJ, Choi SH, Nam SY, et al. Multifocality of papillary thyroid carcinoma as a risk factor for disease recurrence. *Oral Oncol* (2019) 94:106–10. doi: 10.1016/j.oraloncology.2019.05.023
14. Chen HY, Liu WY, Zhu H, Jiang DW, Wang DH, Chen Y, et al. Diagnostic value of contrast-enhanced ultrasound in papillary thyroid microcarcinoma. *Exp Ther Med* (2016) 11(5):1555–62. doi: 10.3892/etm.2016.3094
15. Lee J, Park JH, Lee CR, Chung WY, Park CS. Long-term outcomes of total thyroidectomy versus thyroid lobectomy for papillary thyroid microcarcinoma: comparative analysis after propensity score matching. *Thyroid* (2013) 23(11):1408–15. doi: 10.1089/thy.2012.0463
16. Carty SE, Cooper DS, Doherty GM, Duh QY, Kloos RT, Mandel SJ, et al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. *Thyroid* (2009) 19(11):1153–8. doi: 10.1089/thy.2009.0159
17. Stack BC, Ferris RL, Goldenberg D, Haymart M, Shaha A, Sheth S, et al. American Thyroid Association consensus review and statement regarding the anatomy, terminology, and rationale for lateral neck dissection in differentiated thyroid cancer. *Thyroid* (2012) 22(5):501. doi: 10.1089/thy.2011.0312
18. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): What Changed and Why? *Thyroid* (2017) 27(6):751–6. doi: 10.1089/thy.2017.0102
19. D'Agostino TA, Shuk E, Maloney EK, Zeuren R, Tuttle RM, Bylund CL. Treatment decision making in early-stage papillary thyroid cancer. *Psychooncology* (2018) 27(1):61–8. doi: 10.1002/pon.4383
20. Pelizzo MR, Boschin IM, Toniato A, Piotto A, Bernante P, Pagetta C, et al. Papillary thyroid microcarcinoma (PTMC): prognostic factors, management and outcome in 403 patients. *Eur J Surg Oncol* (2006) 32(10):1144–8. doi: 10.1016/j.ejso.2006.07.001
21. Wang P, Wang Y, Miao C, Yu X, Yan H, Xie Q, et al. Defining a New Tumor Dimension in Staging of Papillary Thyroid Carcinoma. *Ann Surg Oncol* (2017) 24(6):1551–6. doi: 10.1245/s10434-017-5764-z
22. Kiriakopoulos A, Petralias A, Linos D. Multifocal Versus Solitary Papillary Thyroid Carcinoma. *World J Surg* (2016) 40(9):2139–43. doi: 10.1007/s00268-016-3628-5
23. Vorasubin N, Nguyen C, Wang M. Risk factors for cervical lymph node metastasis in papillary thyroid microcarcinoma: A meta-analysis. *Ear Nose Throat J* (2016) 95(2):73–7.
24. Ha SM, Kim JK, Baek JH. Detection of Malignancy Among Suspicious Thyroid Nodules <1 cm on Ultrasound with Various Thyroid Image Reporting and Data Systems. *Thyroid* (2017) 27(10):1307–15. doi: 10.1089/thy.2017.0034
25. Piana S, Frasoldati A, Ferrari M, Valcavi R, Froio E, Barbieri V, et al. Is a five-category reporting scheme for thyroid fine needle aspiration cytology accurate? Experience of over 18,000 FNAs reported at the same institution during 1998-2007. *Cytopathology* (2011) 22(3):164–73. doi: 10.1111/j.1365-2303.2010.00777.x
26. Nayar R, Ivanovic M. The indeterminate thyroid fine-needle aspiration: experience from an academic center using terminology similar to that proposed in the 2007 National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. *Cancer* (2009) 117(3):195–202. doi: 10.1002/cncy.20029
27. Hughes CJ, Shaha AR, Shah JP, Loree TR. Impact of lymph node metastasis in differentiated carcinoma of the thyroid: a matched-pair analysis. *Head Neck* (1996) 18(2):127–32. doi: 10.1002/(SICI)1097-0347(199603/04)18:2<127::AID-HED3>3.0.CO;2-3
28. Lee J, Song Y, Soh EY. Central lymph node metastasis is an important prognostic factor in patients with papillary thyroid microcarcinoma. *J Korean Med Sci* (2014) 29(1):48–52. doi: 10.3346/jkms.2014.29.1.48
29. Beasley NJ, Lee J, Eski S, Walfish P, Witterick I, Freeman JL. Impact of nodal metastases on prognosis in patients with well-differentiated thyroid cancer. *Arch Otolaryngol Head Neck Surg* (2002) 128(7):825–8. doi: 10.1001/archotol.128.7.825
30. Lee KJ, Cho YJ, Kim SJ, Lee SC, Kim JG, Ahn CJ, et al. Analysis of the clinicopathologic features of papillary thyroid microcarcinoma based on 7-mm tumor size. *World J Surg* (2011) 35(2):318–23. doi: 10.1007/s00268-010-0886-5
31. Wang W, Su X, He K, Wang Y, Wang H, Wang H, et al. Comparison of the clinicopathologic features and prognosis of bilateral versus unilateral multifocal papillary thyroid cancer: An updated study with more than 2000 consecutive patients. *Cancer* (2016) 122(2):198–206. doi: 10.1002/cncr.29689
32. Kim HJ, Sohn SY, Jang HW, Kim SW, Chung JH. Multifocality, but not bilaterality, is a predictor of disease recurrence/persistence of papillary thyroid carcinoma. *World J Surg* (2013) 37(2):376–84. doi: 10.1007/s00268-012-1835-2


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 21 October 2020
doi: 10.3389/fendo.2020.577537

# Machine Learning Algorithms for the Prediction of Central Lymph Node Metastasis in Patients With Papillary Thyroid Cancer

*Yijun Wu[1,2†], Ke Rao[1,2†], Jianghao Liu[2], Chang Han[2], Liang Gong[2], Yuming Chong[2], Ziwen Liu[1*] and Xiequn Xu[1*]*

*[1] Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [2] Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China*

OPEN ACCESS

**Edited by:**
*Christoph Reiners, University Hospital Würzburg, Germany*

**Reviewed by:**
*Silvia Martina Ferrari, University of Pisa, Italy*
*Roberto Vita, University of Messina, Italy*

***Correspondence:**
*Xiequn Xu*
*xxq75@163.com*
*Ziwen Liu*
*liuziwenpumch@163.com*

*[†]These authors have contributed equally to this work*

**Specialty section:**
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

**Received:** *29 June 2020*
**Accepted:** *25 September 2020*
**Published:** *21 October 2020*

**Citation:**
*Wu Y, Rao K, Liu J, Han C, Gong L, Chong Y, Liu Z and Xu X (2020) Machine Learning Algorithms for the Prediction of Central Lymph Node Metastasis in Patients With Papillary Thyroid Cancer. Front. Endocrinol. 11:577537. doi: 10.3389/fendo.2020.577537*

**Background:** Central lymph node metastasis (CLNM) occurs frequently in patients with papillary thyroid cancer (PTC), but performing prophylactic central lymph node dissection is still controversial. There are no reliable models for predicting CLNM. This study aimed to develop predictive models for CLNM by machine learning (ML) algorithms.

**Methods:** Patients with PTC who underwent initial thyroid resection at our hospital between January 2018 and December 2019 were enrolled. A total of 22 variables, including clinical characteristics and ultrasonography (US) features, were used for conventional univariate and multivariate analysis and to construct ML-based models. A 5-fold cross validation strategy was used for validation and a feature selection approach was applied to identify risk factors.

**Results:** The areas under the receiver operating characteristic curve (AUC) of 7 models ranged from 0.680 to 0.731. All models performed significantly better than US (AUC=0.623) in predicting CLNM ($P<0.05$). In decision curve, most of the models also performed better than US. The gradient boosting decision tree model with 7 variables was identified as the best model because of its best performance in both ROC (AUC=0.731) and decision curves. Based on multivariate analysis and feature selection, young age, male sex, low serum thyroid peroxidase antibody and US features such as suspected lymph nodes, microcalcification and tumor size > 1.1 cm were the most contributing predictors for CLNM.

**Conclusions:** It is feasible to develop predictive models of CLNM in PTC patients by incorporating clinical characteristics and US features. The ML algorithm may be a useful tool for the prediction of lymph node metastasis in thyroid cancer.

**Keywords: machine learning, cross-validation, central lymph node metastasis, papillary thyroid cancer, feature selection**

## INTRODUCTION

Thyroid cancer is the most common malignant endocrine carcinoma (1, 2). With the rapid advancement of molecular and radiological technologies, the diagnostic accuracy on thyroid cancer has been improved (3). Papillary thyroid cancer (PTC), accounting for 85% to 90% of all thyroid carcinomas, has been increasing in incidence in recent years (4, 5), especially for papillary thyroid microcarcinoma (6). Central lymph node metastasis (CLNM) occurs frequently in PTC, with a prevalence that could be as high as 40% to 90% (7). It was reported that patients with CLNM might be more likely to have distant metastasis and poor survival than those without CLNM (8). Thus, central lymph node dissection (CLND) is required for these patients. However, considering operative complications such as laryngeal nerve paralysis and hypocalcemia caused by the removal of CLND, it is still controversial whether CLND should be performed in all PTC patients. There are also some patients with microscopic and undetectable CLNM who are hard to evaluate by preoperative examination (9), though the significant difference of prognoses among micrometastatic PTC patients who is typically resected with prophylactic CLND appears minimal (10), but whether micrometastases could cause recurrence or distant metastasis remains unclear. Therefore, it is clinically significance to identify patients with a high risk for CLNM before surgery.

Furthermore, central compartment of lymph nodes seems to be the first station of nodal metastasis among thyroid cancer (11). The current approaches to evaluating lymph status before operation mainly included ultrasonography (US) and invasive fine needle aspiration (FNA), though with limited sensitivity (12, 13). There is still lack of more accurate method for identifying the risk of cervical lymph node metastasis. Developing new diagnostic tools for predicting cervical lymph node status is highly necessary.

Machine learning (ML) is a novel computer-based method for data analysis that has been widely applied in clinical medicine (14). ML can find more interactions between variables and outcomes by learning from dataset patterns than conventional statistical methods such as multinomial naïve Bayes (MNB) (15). Since very few studies have developed ML-based predictive models for thyroid cancer, this study aims to construct multiple ML-based models for the preoperative prediction of CLNM and identify risk factors associated with CLNM in patients with PTC.

## MATERIALS AND METHODS

### Patients

This retrospective study was approved by the Ethics Committee of Peking Union Medical College Hospital (PUMCH), and written informed consent was obtained from all patients. A total of 1103 patients who underwent initial thyroid resection in PUMCH between January 2018 and December 2019 were enrolled in this study. All patients had PTC proven by final pathology. The exclusion criteria were as follows: 1) other types of thyroid tumors; 2) undergoing any chemotherapy or radiotherapy for thyroid malignancy before surgery; 3) no CLND; and 4) incomplete clinical information.

### Surgical Approach

For unilateral lobe PTC, lobectomy plus isthmusectomy with ipsilateral CLND was performed. For bilateral PTC or PTC in the isthmus, total thyroidectomy with bilateral CLND was performed. If lateral lymph node metastasis was suspected by preoperative ultrasound or proved by fine-needle aspiration cytology, lateral lymph node dissection was also performed. The dissection of the central compartment was considered level VI and included the pretracheal, paratracheal, and prelaryngeal lymph nodes. The lateral lymph nodes involve levels II, III, IV, and V. All surgical specimens were identified through intraoperative frozen section and postoperative paraffin section examination by pathological experts from PUMCH.

### Clinical Characteristics and Ultrasonographical Features

The following clinical characteristics were retrospectively collected for analysis: age, sex, body mass index (BMI), mean arterial pressure (MAP), fasting blood glucose (FBG) and thyroid function test results. All data were recorded before operation. Thyroid function tests were performed within one month before the operation at our hospital and included assessments of triiodothyronine (T3), tetraiodothyronine (T4), free T3 (FT3), free T4 (FT4), thyroid stimulating hormone (TSH), thyroid peroxidase antibody (TPO-Ab) and thyroglobulin antibody (TG-Ab).

All patients underwent cervical US within one month before surgery at our hospital with Phillips IU 22 (Philips Healthcare, Eindhoven, Netherlands), GE Logiq 9 (GE Healthcare, Milwaukee, WI, USA) devices equipped with 5 to 12MHz linear-array transducer (Thermal Index in soft tissue=0.1, Mechanical Index=0.06). There were only few patients that also underwent cervical computed tomography (CT) and FNA, which were performed if necessary, and thus the findings of CT and FNA were not included in this study. Based on US, the following features were recorded: tumor size, tumor location, hypoechogenicity, multiple nodules, bilateral nodules, microcalcification, irregular shape, unclear margin and capsular invasion. Tumor size was defined as the maximal tumor diameter for unifocal cases and as the maximal diameter of the largest tumor for multifocal cases (16, 17). Tumor location was divided into two areas (left or right lobe, and isthmus). Classification of internal echogenicity was made as hypoechogenicity (totally solid) or non-hypoechogenicity (including mixed cystic, solid and iso-echoic nodules). The presence of multiple nodules was confirmed when there were other nodules (benign or malignant) in the thyroid in addition to the primary tumor. On a special occasion, when the additional nodules located in the contralateral lobe of the primary tumor, they were called bilateral nodules. Microcalcifications were defined as punctate echogenic foci ≤ 1 mm inside tumors.

Classification of tumor shape was made as regular or irregular. Unclear margin was confirmed when the tumor nodules' margin could not be well defined under US. Capsular invasion was defined as the disruption of the perithyroidal echogenic line between the thyroid capsule and the tumor. In addition, the metastatic status of cervical lymph nodes (LNs) on US was also included, which was based on multiple characteristics of lymph nodes, including size, shape, margin, cortex, echogenicity, echotexture, microcalcification, necrosis, hilar echogenicity and vascularity (18). For cases with multifocal thyroid tumors, some features such as hypoechogenicity, microcalcification, irregular shape, unclear margin and capsular invasion were identified if they were observed in any one of the tumors. All of the US features above were assessed by sonographers at our hospital with more than 10 years of experience in analyzing US image of thyroid cancer.

## Development of ML-Based Models

A total of 22 variables involving clinical characteristics and US features (**Table 2**) were used to develop ML-based models for the preoperative prediction of CLMN. Seven algorithms were applied in this study, including six representative supervised ML algorithms [random forest classifier (RFC), artificial neural network (ANN), decision tree (DT), gradient boosting decision tree (GBDT), extreme gradient boosting (XGBoost) and adaptive boosting (AdaBoost)] (19–24) and the conventional algorithms (MNB). Most of the algorithms are inexplicable except DT and MNB, in which the function between variables and the outcome cannot be visible to users. The ANN algorithm is a widely parallel inter-connected network composed of adaptable simple units, which can simulate the interaction of the biological nervous system with real-world objects. The DT algorithm divides a difficult prediction problem into two or more simpler subsets like branches of the tree, and thus into different sub-problems structurally. RFC is a more advanced algorithm based on DT, which can used for both regression and classification. GBDT, XGBoost and AdaBoost fall into one kind of important ML algorithms called ensemble learning. It can improve the generalization ability of the classifiers by training multiple classifiers and then combining them to achieve better prediction performance. Moreover, to construct more reliable models, all continuous variables underwent preprocessing for z-score normalization, except for MNB, in which min-max normalization is preferred (25).

The predictive performance of these models was evaluated by the area under the receiver operating characteristic (ROC) curve (AUC). In addition, decision curve analysis (DCA) was used to assess the clinical utility of these models. The predictive performance of cervical US for CLNM was also evaluated and compared with that of the models using a t-test.

## Validation Strategy and Feature Selection

To minimize the adverse effect of overfitting, a common problem in ML algorithms, 5-fold cross-validation and feature selection were performed (26, 27). A classifier-specific importance evaluator was applied to identify the optimal variables for each model (28). A ranked list of variables was generated for each model, and all of the variables were compared to determine their predictive importance for CLNM. The AUCs of different numbers of variables were also calculated to find the optimal dimension (number of variables) of each model.

## Statistical Analysis

Univariate and multivariate analysis (LR forward) was performed using IBM SPSS 25.0 (SPSS Inc; Chicago, IL, USA). The development and validation of ML-based models were performed using Python programming language (version 3.7, Python Software Foundation). Student's t-test was used to compare models' predictive performance (AUC). The normality of quantitative data was tested by the Shapiro-Wilk test. Non-normally distributed data are expressed as the median with interquartile range (IQR). Normally distributed quantitative parameters were compared by Student's t-test, while non-normally distributed parameters were compared by the Mann-Whitney U test. For categorical data, Pearson's chi square test was applied. A P value $< 0.05$ was considered statistically significant.

# RESULTS

## Demographic Characteristics

As shown in **Table 1**, this retrospective study cohort consisted of 297 (26.9%) males and 806 (73.1%) females, with a median age of 41 (IQR: 33–51) years. Of all patients, the median BMI, MAP, FBG and tumor size were 24.33 (IQR: 21.97–26.67), 93 mmHg

**TABLE 1** | Demographic characteristics of the patients.

| Clinicopathological characteristics | Data |
|---|---|
| All patients, n (%) | 1103 (100.0) |
| Age, years† | 41 (33–51) |
| Sex, n (%) | |
| Male | 297 (26.9) |
| Female | 806 (73.1) |
| BMI† | 24.33 (21.97–26.67) |
| MAP, mmHg† | 93 (86–102) |
| FBG, mmol/L† | 5.1 (4.8–5.5) |
| Tumor size, cm† | 1.0 (0.7–1.5) |
| ≤ 1.0 | 560 (50.8) |
| 1.0–2.0 | 385 (34.9) |
| ≥ 2.0 | 158 (14.3) |
| Multiple nodules, n (%) | |
| Yes | 660 (59.8) |
| No | 443 (40.2) |
| Bilateral nodules, n (%) | |
| Yes | 542 (49.1) |
| No | 561 (50.9) |
| Central lymph node metastasis | |
| Positive | 612 (55.5) |
| Negative | 491 (44.5) |
| Surgical resection, n (%) | |
| Lobectomy plus isthmusectomy with ipsilateral CLND | 439 (39.8) |
| Total thyroidectomy with bilateral CLND | 664 (60.2) |
| No. of harvested central lymph nodes† | 7 (5–11) |
| No. of positive central lymph nodes† | 3 (1–5) |

†*Continuous variables were expressed as median with interquartile range.*
*BMI, body mass index; MAP, mean arterial pressure; FBG, fasting blood glucose; CLND, central lymph node dissection.*

**TABLE 2** | Univariate analysis of clinical characteristics and ultrasonography features related to central lymph node metastasis (CLMN).

| Variable | Univariate analysis | | |
|---|---|---|---|
| | CLMN (–) | CLMN (+) | P value |
| Age, years† | 45 (37–53) | 38 (31–47) | <0.001 |
| Sex, n (%) | | | |
| Male | 109 (22.2) | 188 (30.7) | 0.002 |
| Female | 382 (77.8) | 424 (69.3) | |
| BMI† | 24.46 (22.06–26.45) | 24.22 (21.76–26.83) | 0.764 |
| MAP, mmHg† | 94 (86–103) | 93 (86–101) | 0.295 |
| FBG, mmol/L† | 5.2 (4.9–5.6) | 5.1 (4.8–5.5) | 0.004 |
| FT3, pg/ml† | 3.06 (2.82–3.28) | 3.15 (2.91–3.36) | <0.001 |
| FT4, ng/dl† | 1.21 (1.01–1.31) | 1.22 (1.13–1.33) | 0.048 |
| T3, pg/ml† | 1.04 (0.94–1.14) | 1.04 (0.95–1.17) | 0.247 |
| T4, ng/dl† | 7.90 (7.00–8.90) | 7.63 (6.90–8.70) | 0.090 |
| TSH, μIU/ml† | 1.72 (1.20–2.64) | 1.76 (1.22–2.62) | 0.941 |
| TG-Ab, IU/ml† | 13.69 (10.43–83.94) | 13.17 (10.30–74.00) | 0.467 |
| TPO-Ab, IU/ml† | 14.91 (12.04–23.84) | 13.90 (11.47–19.67) | 0.027 |
| **Ultrasonography features** | | | |
| Tumor size, cm† | 0.9 (0.7–1.3) | 1.2 (0.9–1.7) | <0.001 |
| Tumor location, n (%) | | | |
| Left or right lobe | 471 (95.9) | 590 (96.4) | 0.680 |
| Isthmus | 20 (4.1) | 22 (3.6) | |
| Hypoechogenicity, n (%) | | | |
| Yes | 438 (89.2) | 554 (90.5) | 0.470 |
| No | 53 (10.8) | 58 (9.5) | |
| Multiple nodules, n (%) | | | |
| Yes | 306 (62.3) | 354 (57.8) | 0.132 |
| No | 185 (37.7) | 258 (42.2) | |
| Bilateral nodules, n (%) | | | |
| Yes | 253 (51.5) | 289 (47.2) | 0.155 |
| No | 238 (48.5) | 323 (52.8) | |
| Microcalcification, n (%) | | | |
| Present | 252 (51.3) | 442 (72.2) | <0.001 |
| Absent | 239 (48.7) | 170 (27.8) | |
| Irregular shape, n (%) | | | |
| Yes | 328 (66.8) | 452 (73.9) | 0.011 |
| No | 163 (33.2) | 160 (26.1) | |
| Unclear margin, n (%) | | | |
| Yes | 336 (68.4) | 439 (71.7) | 0.233 |
| No | 155 (31.6) | 173 (28.3) | |
| Capsular invasion, n (%) | | | |
| Yes | 38 (7.7) | 61 (10.0) | 0.198 |
| No | 453 (92.3) | 551 (90.0) | |
| Suspected LNs, n (%) | | | |
| Present | 81 (16.5) | 251 (41.0) | <0.001 |
| Absent | 410 (83.5) | 361 (59.0) | |

†*Continuous variables were expressed as median with interquartile range.*
*BMI, body mass index; MAP, mean arterial pressure; FBG, fasting blood glucose; T3, triiodothyronine; T4, tetraiodothyronine; FT3, free T3; FT4, free T4; TSH, thyroid stimulating hormone; TPO-Ab, thyroid peroxidase antibody; TG-Ab, thyroglobulin antibody; LNs, lymph nodes.*

(IQR: 86–102), 5.1 mmol/L (IQR: 4.8–5.5), and 1.0 cm (IQR: 0.7–1.5), respectively. There were 560 (50.8%) patients with tumors ≤ 1.0 cm, 385 (34.9%) patients with tumors 1.0 to 2.0 cm and 158 (14.3%) patients with tumors ≥ 2.0 cm. The presence of multiple nodules was observed in 660 (59.8%) cases, and bilateral nodules were observed in 542 (49.1%) cases. A total of 612 (55.5%) patients were proven to have positive central LNs by postoperative pathology. There were 439 (39.8%) patients who underwent lobectomy plus isthmusectomy with ipsilateral CLND and 664 (60.2%) who underwent total thyroidectomy with bilateral CLND. The median number of harvested central LNs was 7 (IQR: 5–11), while that of positive central LNs was 3 (IQR: 1–5).

## Univariate and Multivariate Analyses of Variables

Univariate analysis (**Table 2**) showed that CLNM was significantly associated with age, sex, FBG, FT3, FT4, TPO-Ab and US features such as tumor size, microcalcification, irregular shape and suspected LNs (P<0.05). Then, variables with P<0.05 in the univariate analysis were selected for multivariate analysis using LR forward stepwise selection. The results showed that age (OR=0.959, 95% CI: 0.948–0.971, P<0.001), male sex (vs. female, OR=1.527, 95% CI: 1.132–2.059, P=0.006), TPO-Ab (OR=0.998, 95% CI: 0.997–0.999, P=0.003) and US features such as tumor size (OR=1.234, 95% CI: 1.058–1.439, P=0.007), microcalcification (OR=1.911, 95% CI: 1.461–2.500, P<0.001) and suspected LNs (OR=3.268, 95% CI: 2.401–4.448, P<0.001) were independent risk factors for CLNM (**Table 3**).

## Predictive Performance and Clinical Usefulness of ML-Based Models

Using all 22 variables, predictive models for CLNM were developed based on 7 algorithms. The predictive performance of the models is shown in **Figure 1** and **Table 4**. All models we developed performed significantly better than US (AUC=0.623, SD=0.017, P<0.05). The AUC values of ML models were higher than the conventional MNB except DT and XGBoost, though the differences were not significant (P>0.05).

To evaluate the clinical utility of these models, DCA was performed (**Figure 2**). According to the incidence of CLNM among patients with PTC, the reasonable range of thresholds was set as 0.4 to 0.9. Almost at the entire range, all ML-based models showed higher net benefits than the two extreme lines (treat-none and treat-all) except AdaBoost. It was noteworthy that three ML-based model, GBDT, ANN and RFC, always performed better than US and other models. There were sharply decreases at the threshold range of 0.7 to 0.9 for ANN and 0.6 to 0.8 for RFC, but the GBDT model remained a stably-high net benefit across almost the entire reasonable range of threshold probabilities.

**TABLE 3** | Multivariate analysis of clinical characteristics and ultrasonography features related to central lymph node metastasis (CLMN).

| Variable | OR | 95% CI | P value |
|---|---|---|---|
| Age | 0.959 | 0.948–0.971 | <0.001 |
| Sex | | | |
| Male | 1.527 | 1.132–2.059 | 0.006 |
| Female | Reference | – | – |
| TPO-Ab | 0.998 | 0.997–0.999 | 0.003 |
| Tumor size | 1.234 | 1.058–1.439 | 0.007 |
| Microcalcification | 1.911 | 1.461–2.500 | <0.001 |
| Suspected LNs | 3.268 | 2.401–4.448 | <0.001 |

*TPO-Ab, thyroid peroxidase antibody; LNs, lymph nodes.*

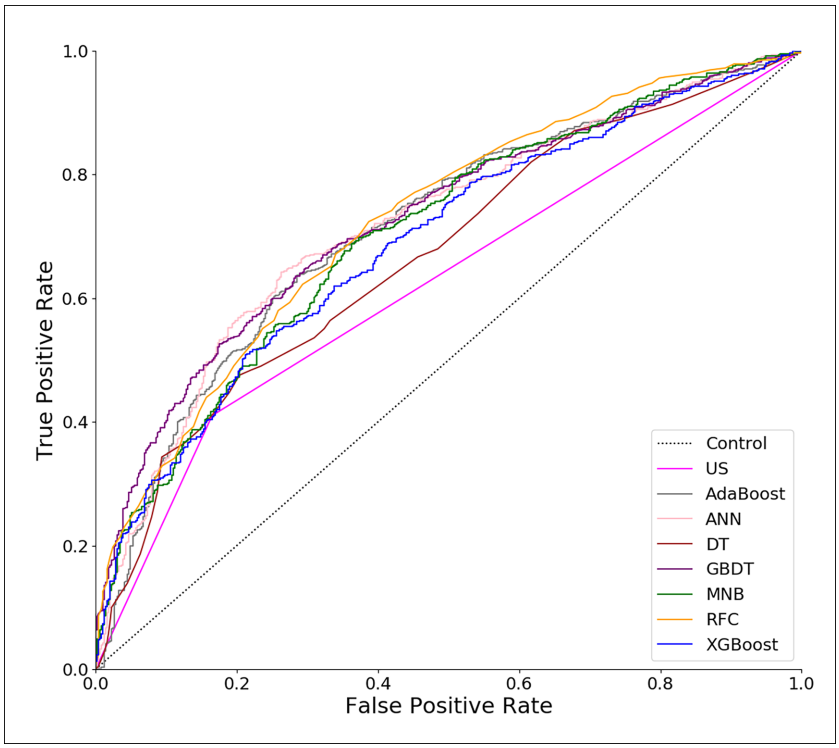


**FIGURE 1** | Receiver operating characteristic (ROC) curves of predictive models based on machine learning algorithms. US, ultrasonography; GBDT, gradient boosting decision tree; RFC, random forest classifier; AdaBoost, adaptive boosting; ANN, artificial neural network; MNB, multinomial naïve Bayes; XGBoost, extreme gradient boosting; DT, decision tree.

## Variable Importance

With favorable AUCs and clinical benefits according to the DCA, GBDT, RFC and ANN were selected to be the models with the most potential for predicting CLNM in PTC patients. By the feature selection approach, the top 10 variables were ranked based on their predictive importance in each potential model (**Figure 3**). The variables were arranged in order of mean ranking: suspected LNs, tumor size, age, microcalcification, gender, TPO-Ab, TSH, irregular shape, hypoechogenicity, and capsular invasion. The ranks of each variable in different models were described in **Supplementary Table 1**.

GBDT was identified as the best predictive model in this study because of its best performance in both ROC curve (**Figure 1**) and decision curve (**Figure 2**). The AUCs of GBDT reached the highest when 7 variables were introduced (**Figure 4**). These 7 variables were as follows: age, suspected LNs, tumor size, microcalcification, irregular shape, TPO-Ab and TSH.

**TABLE 4** | Predictive performance of models and ultrasonography alone and their optimal number of dimensions (number of variables).

| Model | AUC | | | No. of optimal dimension | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| | Mean | SD | P value† | | | |
| GBDT | 0.731 | 0.015 | <0.001 | 7 | 63.6% | 71.7% |
| RFC | 0.730 | 0.015 | <0.001 | 12 | 72.4% | 61.3% |
| AdaBoost | 0.721 | 0.015 | <0.001 | 8 | 63.7% | 71.5% |
| ANN | 0.718 | 0.015 | <0.001 | 5 | 64.2% | 73.7% |
| MNB | 0.717 | 0.016 | <0.001 | 5 | 69.8% | 62.7% |
| XGBoost | 0.690 | 0.016 | 0.002 | 14 | 51.0% | 78.6% |
| DT | 0.680 | 0.016 | 0.008 | 3 | 47.5% | 79.6% |
| US | 0.623 | 0.017 | – | 1 | 41.0% | 83.5% |

*†P values were obtained when compared with US. Sensitivity and specificity were confirmed according to maximal Youden's index.*

*AUC, area under the curve; SD, standard deviation; GBDT, gradient boosting decision tree; RFC, random forest classifier; AdaBoost, adaptive boosting; ANN, artificial neural network; MNB, multinomial naïve Bayes; XGBoost, extreme gradient boosting; DT, decision tree; US, ultrasonography.*

## DISCUSSION

Currently, the prevalence of PTC has shown rapid growth as US has been widely used for cervical examination. Despite the fact that patients with PTC have a 10-year survival rate of more than 90% (29), lymph node metastasis occurs very frequently. The central compartment is regarded as the first metastatic station, whose metastatic incidence could reach up to 90% (7). Previous studies have shown that CLNM was significantly associated with local recurrence and survival (8, 30, 31). Then, prophylactic CLND was proposed, but this procedure would be irrelevant for patients without nodal metastasis and even cause a higher

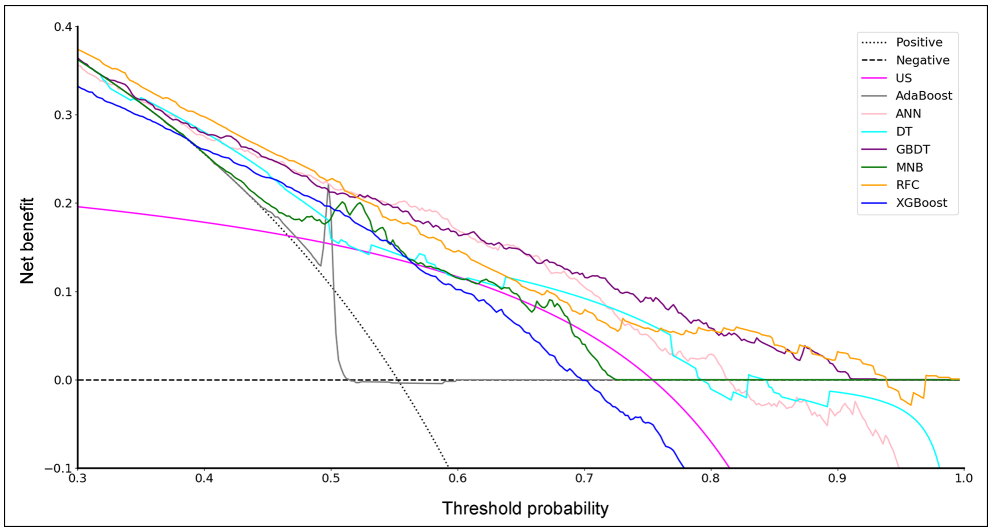


**FIGURE 2** | Decision curve for predictive models based on machine learning algorithms. US, ultrasonography; GBDT, gradient boosting decision tree; RFC, random forest classifier; AdaBoost, adaptive boosting; ANN, artificial neural network; MNB, multinomial naïve Bayes; XGBoost, extreme gradient boosting; DT, decision tree.

incidence of complications. Thus far, whether to perform CLND for PTC patients without preoperative and intraoperative suspected lymph node metastasis remains controversial. There are no reliable predictive models for CLNM in PTC patients. Therefore, in addition to univariate and multivariate analysis, we developed multiple models for the prediction of CLNM by ML algorithms and compared these models with US. ROC analysis and DCA were used to assess these models' predictive performance and clinical utility, respectively. Then, potential models were confirmed to identify risk factors for CLNM by feature selection.

In this study, a retrospective cohort of 1103 PTC patients was reviewed. A total of 22 variables including clinical characteristics and US features were used to predict CLNM. The predictive performance of all models was significantly better than that of US (**Table 4**). The three excellent models, including GBDT, RFC and ANN, performed better in both the ROC analysis and DCA than the other models (**Table 4**, **Figures 1** and **2**).

Despite the invisible connection between variables and outcomes in most ML-based models, the predictive importance of the variables in each potential model was obtained by using the classifier-specific evaluator (**Figure 3**). Thus, the top ten variables were considered to be the most important risk factors for CLNM: suspected LNs, tumor size, age, microcalcification, gender, TPO-Ab, TSH, irregular shape, hypoechogenicity and capsular invasion.

Currently, the definitive diagnosis of CLNM mainly depends on postoperative pathology. The preoperative risk factors for CLNM in PTC patients remain unclear. Our study suggested that CLNM had a significant tendency to appear in young patients. The optimal cut-off age was 40 years old (AUC=0.648; sensitivity: 0.68; specificity: 0.56), which is similar to previous studies that reported age < 45 years was a risk factor for CLNM (16, 17, 32, 33). In addition, a sex predisposition was also observed in our study. We found that males were associated with a higher incidence of CLNM, which was also supported by previous reports (16, 17, 32–35). Overall, male patients < 40 years old might be considered a high-risk population for CLNM and should be evaluated carefully when choosing surgical procedures. In addition, TPO-Ab was also identified as an independent risk factor by multiple analysis and ML algorithms. Actually, several studies have reported the association between nodal metastasis and chronic lymphocytic thyroiditis (CLT), which can demonstrate an increased serum level of TPO-Ab. A meta-analysis from Lee et al. concluded that CLT occurred more in PTC patients but might indicated no lymph node metastasis. However, Antonio et al. found the coexistence of CLT among PTC patients was associated with more risk of nodal metastasis. On the other hand, very few studies focused on the association between TPO-Ab and CLNM. In our study, we found that a reduced serum TPO-Ab level might indicate a high risk for CLNM, but this association still requires further confirmation of future prospective studies. The TSH value was not significantly different between CLNM (+) and CLNM (–) patients in our study or previous studies (16), but this variable was ranked 7th according to the mean rankings of three potential models (**Figure 3**). TSH was also involved in the GBDT model with a rank of 7. This might also indicate the superiority of ML algorithms on data mining and reveal that variables having a P value > 0.5 in the use of conventional statistical methods should not be totally overlooked.

Previously, the sensitivity of US in predicting LNM was reported to be as low as 41.3% to 61.0%, although US is most commonly used for the assessment of cervical LNs (36–38). Other imaging examinations, such as CT, performed slightly better in terms of sensitivity than US, but the difference was not significant (37, 38). In our study, all patients underwent preoperative US, which showed that 332 (30.1%) patients

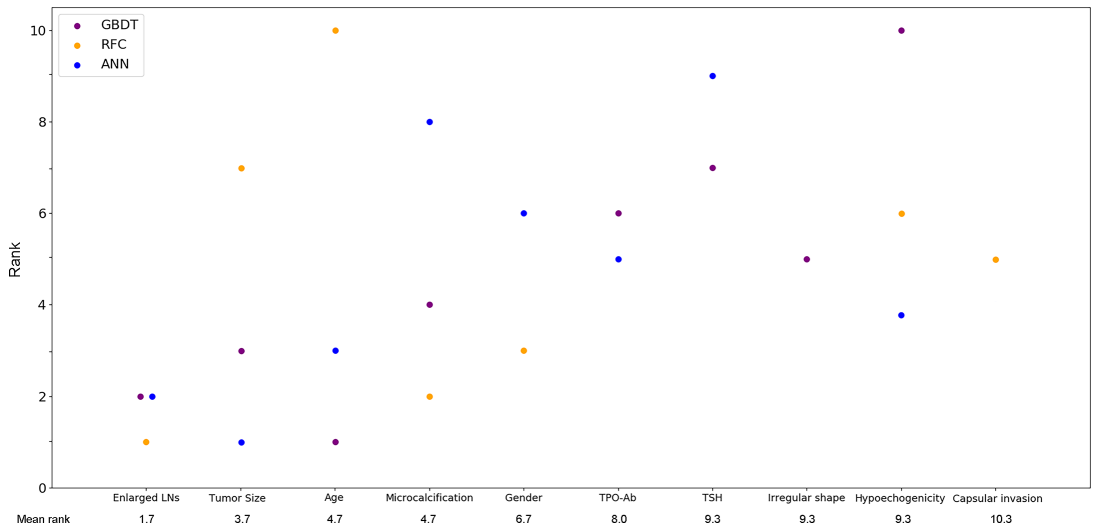


**FIGURE 3** | Ranks of the top 10 variables for the prediction of central lymph node metastasis. Variables were ranked using a classifier-specific importance evaluator based on machine learning algorithms. The variables are ordered according to the mean ranking of three potential models, which were GBDT, RFC and ANN. A lower rank represents more predictive importance. For example, age was ranked 1st, 3rd, and 10th in GBDT, ANN, and RFC, respectively. LNs, lymph nodes; Micro-Cal, microcalcification; TPO-Ab, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; Ir. shape, irregular shape; Cap. invasion, capsular invasion; Hypo-echo, hypoechogenicity; GBDT, gradient boosting decision tree; RFC, random forest classifier; ANN, artificial neural network.

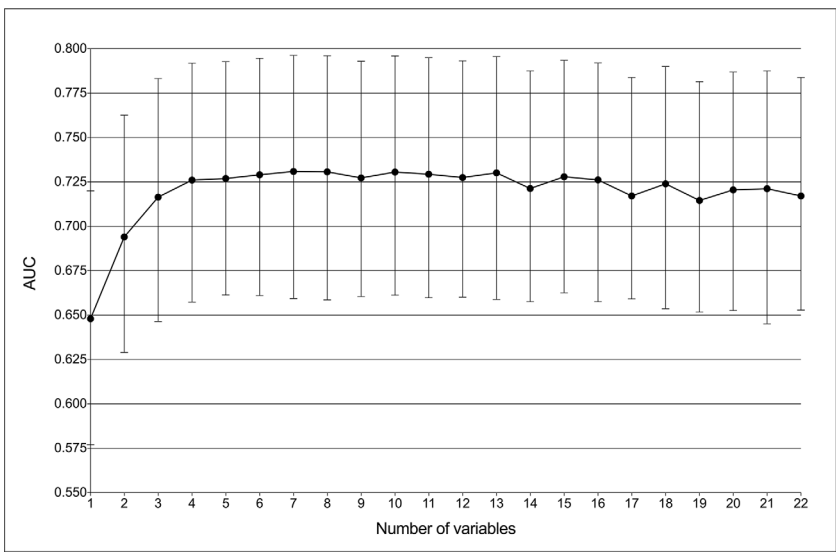


**FIGURE 4** | Predictive performance of the gradient boosting decision tree (GBDT) model with different numbers of variables. The AUC was the highest (0.731) with seven variables.

possessed suspected LNs (AUC=0.623; sensitivity: 0.41; specificity: 0.83). Moreover, the presence of suspected LNs was also identified as the most predictive risk factor for CLNM based on ML models. Thus, the previous suggestion that all patients with suspected lymph nodes on US should undergo CLND is reasonable, but US alone is still not enough to predict CLNM status. Tumor size on US images is an important indicator of tumor growth. It has been reported that large tumor size was an independent risk factor for CLNM, but the cut-off values are inconsistent. Liu and Ahn et al. thought that tumors > 1.0 cm were a risk factor for CLNM (16, 17), while Zhou et al. suggested a tumor size threshold > 0.7 cm (39). Our study also indicated that tumor size was an independent risk factor for CLNM (**Table 3**), and this variable ranked third in mean ranking of ML models

(**Figure 3**). The optimal cut-off tumor size was calculated to be > 1.1 cm (AUC=0.634; sensitivity: 0.59; specificity: 0.37), which is almost consistent with that in previous reports (16, 17). In addition, microcalcification on US images also indicated CLNM. Eun et al. classified calcifications inside thyroid carcinoma into four types: microcalcification, macrocalcification, rim calcification and non-calcification (40). Many studies have reported that the presence of microcalcification was significantly associated with a higher incidence of cervical LNM (16, 40, 41). It is thought that the formation of microcalcifications is caused by the rapid proliferation of cancer cells (42). Therefore, PTC patients with the presence of microcalcification on US images should be evaluated more carefully before surgery. Furthermore, irregular shape, capsular invasion and hypoechogenicity might be potential risk factors for CLNM. Tumors with these US features deserve more attention.

In addition to the clinical indications, there were some methodological innovations in this study. First, this is the first study to develop ML-based models for the prediction of CLNM in PTC patients. By incorporating clinical characteristics and US features, these ML-based models showed excellent predictive performance and clinical utility by ROC analysis and DCA. Second, in addition to conventional multivariate analysis, using feature selection approach, we identified risk factors for CLNM by mean ranking three well-selected ML-based models. The mean ranks of these variables indicated their predictive importance. Third, our study identified the best ML-based model for the prediction of CLNM in PTC patients, which was the GBDT model with 7 variables. In the future, an online application of the GBDT model should be developed based on the clinical characteristics and US features to allow surgeons and patients in other hospitals to benefit from this study.

Several limitations were needed to be noted. First, this is a retrospective study in which data bias might be unavoidable. A prospective cohort should be used to construct an ML-based model for further evaluation. Second, more than 50% of the tumors included were microcarcinomas (≤ 1 cm). Actually, many other centers do not biopsy or operate on thyroid nodules less than 1 cm, which limited the reproducibility of this study.

## CONCLUSIONS

Using ML algorithms, it is feasible to incorporate clinical characteristics and US features to predict CLNM in PTC patients. All ML-based models performed better than US in the prediction of CLNM. The GBDT model with 7 variables was identified as the best model according to ROC analysis and DCA. Based on multivariate analysis and feature selection, younger age, male sex, low serum TPO-Ab and US features such as suspected LNs, microcalcifications and tumor size > 1.1 cm were important risk factors for CLNM. ML algorithms can be useful for the prediction of lymph node metastasis in PTC.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Peking Union Medical College Hospital. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

Conceptualization: ZL, XX, YW, and KR. Methodology: YW, CH, and. JL. Formal analysis: YW, KR, CH, JL, YC, and LG. Investigation: YW, KR, and LG. Writing—original draft preparation: YW. Writing—review and editing: YW, KR, ZL, and XX. Supervision: YW and XX. All authors contributed to the article and approved the submitted version.

## ACKNOWLEDGMENTS

We would like to thank American Journal Experts (www.aje.com) for the linguistic assistance to this manuscript from.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2020.577537/full#supplementary-material

## REFERENCES

1. Wiltshire JJ, Drake TM, Uttley L, Balasubramanian SP. Systematic Review of Trends in the Incidence Rates of Thyroid Cancer. *Thyroid* (2016) 26 (11):1541–52. doi: 10.1089/thy.2016.0100
2. Morris LGT, Sikora AG, Tosteson TD, Davies L. The increasing incidence of thyroid cancer: the influence of access to care. *Thyroid* (2013) 23(7):885–91. doi: 10.1089/thy.2013.0045
3. Ferrari SM, Fallahi P, Ruffilli I, Elia G, Ragusa F, Paparo SR, et al. Molecular testing in the diagnosis of differentiated thyroid carcinomas. *Gland Surg* (2018) 7(Suppl 1):S19–29. doi: 10.21037/gs.2017.11.07
4. La Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F, et al. cancer: Thyroid cancer mortality and incidence: a global overview. *Int J Cancer* (2015) 136(9):2187–95. doi: 10.1002/ijc.29251
5. Cabanillas ME, McFadden DG, Durante. Thyroid cancer. *Lancet* (2016) 388 (10061):2783–95. doi: 10.1016/s0140-6736(16)30172-6
6. Slijepcevic N, Zivaljevic V, Marinkovic J, Sipetic S, Diklic A, Paunovic I. Retrospective evaluation of the incidental finding of 403 papillary thyroid microcarcinomas in 2466 patients undergoing thyroid surgery for presumed benign thyroid disease. *BMC Cancer* (2015) 15:330–0. doi: 10.1186/s12885-015-1352-4
7. Lundgren CI, Hall P, Dickman PW, Zedenius J. Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based,

nested case-control study. *Cancer* (2006) 106(3):524–31. doi: 10.1002/cncr.21653
8. Chen L, Zhu Y, Zheng K, Zhang H, Guo H, Zhang L, et al. The presence of cancerous nodules in lymph nodes is a novel indicator of distant metastasis and poor survival in patients with papillary thyroid carcinoma. *Res c. Oncol* (2017) 143(6):1035–42. doi: 10.1007/s00432-017-2345-2
9. Bardet S, Ciappuccini R, Quak E, Rame J-P, Blanchard D, de Raucourt D, et al. Prognostic value of microscopic lymph node involvement in patients with papillary thyroid cancer. *Endocrinol Metab* (2015) 100(1):132–40. doi: 10.1210/jc.2014-1199
10. Patel KN, Yip L, Lubitz CC, Grubbs EG, Carty SE. The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Thyroid Disease in Adults. *Surgery* (2020) 271(3):e21–93. doi: 10.1097/sla.0000000000003580
11. Kim YS. Patterns and predictive factors of lateral lymph node metastasis in papillary thyroid microcarcinoma. *Otolaryngology-Head N Surg* (2012) 147(1):15–9. doi: 10.1177/0194599812439277
12. Kim E, Park JS, Son K-R, Kim J-H, Jeon SJ, Na DG. Preoperative diagnosis of cervical metastatic lymph nodes in papillary thyroid carcinoma: comparison of ultrasound, computed tomography, and combined ultrasound with computed tomography. *Thyroid* (2008) 18(4):411–8. doi: 10.1089/thy.2007.0269
13. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al. Ultrasonographically and anatomopathologically detectable node metastases in the lateral compartment as indicators of worse relapse-free survival in patients with papillary thyroid carcinoma. *World J Surg* (2005) 29(7):917–20. doi: 10.1007/s00268-005-7789-x
14. Deo RC. Machine Learning in Medicine. *Circulation* (2015) 132(20):1920–30. doi: 10.1161/circulationaha.115.001593
15. Shouval R, Bondi O, Mishan H, Shimoni A, Unger R, Nagler A, et al. Application of machine learning algorithms for clinical predictive modeling: a data-mining approach in SCT. *Bone Marrow Transplant* (2014) 49(3):332–7. doi: 10.1038/bmt.2013.146
16. 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. doi: 10.1186/s12885-019-5835-6
17. Ahn BH, Kim JR, Jeong HC, Lee JS, Chang ES, Kim YH. Predictive factors of central lymph node metastasis in papillary thyroid carcinoma. *Ann Surg Treat Res* (2015) 88(2):63–8. doi: 10.4174/astr.2015.88.2.63
18. Marrocos Machado MR, Tavares MR, Buchpiguel CA, Chammas MC. Ultrasonographic Evaluation of Cervical Lymph Nodes in Thyroid Cancer. *Otolaryngol Head Neck Surg* (2017) 156(2):263–71. doi: 10.1177/0194599816676472
19. Ngiam KY, Khor IW. Big data and machine learning algorithms for health-care delivery. *Lancet Oncol* (2019) 20(5):e262–73. doi: 10.1016/S1470-2045(19)30149-4
20. Gonzalez GH, Tahsin T, Goodale BC, Greene AC, Greene CS. Recent Advances and Emerging Applications in Text and Data Mining for Biomedical Discovery. *Briefings Bioinf* (2016) 17(1):33–42. doi: 10.1093/bib/bbv087
21. Breiman L. Random forests. *Mach Learn* (2001) 45(1):5–32. doi: 10.1023/A:1010933404324
22. Schapire RE. A short introduction to boosting. *Jinko Chino Gakkaishi* (1999) 14:1612.
23. Freund Y, Mason L. The alternating decision tree learning algorithm. *ICML* (1999) 99:124–33.
24. Chen T, Guestrin C. *Xgboost: A scalable tree boosting system. Proceedings of the 22nd acm sigkdd international conference on knowledge discovery and data mining, ACM*. (2016). pp. 785–94.
25. Shalabi. LA, Shaaban. Z, Kasasbeh B. Data Mining: A Preprocessing Engine. *J Comput Sci* (2006) 2(9):735–9. doi: 10.3844/jcssp.2006.735.739
26. Jung Y. Multiple predicting K-fold cross-validation for model selection. *J Nonparametr Stat* (2018) 30(1):197–215. doi: 10.1080/10485252.2017.1404598
27. Cook JA, Ranstam J. Overfitting. *BJS* (2016) 103:1804–14. doi: 10.1002/bjs.10244
28. Rodriguez-Galiano VF, Luque-Espinar JA, Chica-Olmo M, Mendes MP. Feature selection approaches for predictive modelling of groundwater nitrate pollution: An evaluation of filters, embedded and wrapper methods. *Sci Total Environ* (2018) 624:661–72. doi: 10.1016/j.scitotenv.2017.12.152
29. Malterling RR, Andersson RE, Falkmer S, Falkmer U, Niléhn E. Differentiated thyroid cancer in a Swedish county–long-term results and quality of life. *Acta Oncol* (2010) 49(4):454–9. doi: 10.3109/02841860903544600
30. Ito Y, Jikuzono T, Higashiyama T, Asahi S, Tomoda C, Takamura. Y, et al. Clinical significance of lymph node metastasis of thyroid papillary carcinoma located in one lobe. *World J Surg* (2006) 30(10):1821–8. doi: 10.1007/s00268-006-0211-5
31. Adam MA, Pura J, Goffredo P, Dinan MA, Sosa JA. Presence and Number of Lymph Node Metastases Are Associated With Compromised Survival for Patients Younger Than Age 45 Years With Papillary Thyroid Cancer. *J Clin Oncol* (2015) 33(21):2370–5. doi: 10.1200/jco.2014.59.8391
32. Yan H, Zhou X, Jin H, Li X, Zheng M, Ming X, et al. A Study on Central Lymph Node Metastasis in 543 cN0 Papillary Thyroid Carcinoma Patients. *Int J Endocrinol* (2016) 2016:1878194. doi: 10.1155/2016/1878194
33. Qu N, Lin D-Z, Shi R-L, Lu Z-W, Ji Q-H, Wu W-L. Risk prediction and clinical model building for lymph node metastasis in papillary thyroid microcarcinoma. *Onco Targets Ther* (2016) 9:5307–16. doi: 10.2147/ott.S107913
34. Zhang L, Wei W-J, Ji Q-H, Zhu Y-X, Wang Z-Y, Wang Y, et al. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. *J Clin Endocrinol Metab* (2012) 97(4):1250–7. doi: 10.1210/jc.2011-1546
35. Ahn JE, Lee JH, Yi JS, Shong YK, Hong SJ, Lee DH, et al. Diagnostic accuracy of CT and ultrasonography for evaluating metastatic cervical lymph nodes in patients with thyroid cancer. *World J Surg* (2008) 32(7):1552–8. doi: 10.1007/s00268-008-9588-7
36. Roh J-L, Park J-Y, Kim J-M, Song C-J. Use of preoperative ultrasonography as guidance for neck dissection in patients with papillary thyroid carcinoma. *J Surg Oncol* (2009) 99(1):28–31. doi: 10.1002/jso.21164
37. Jeong H-S, Baek C-H, Son Y-I, Choi J-Y, Kim H-J, Ko. Y-H, et al. Integrated 18F-FDG PET/CT for the initial evaluation of cervical node level of patients with papillary thyroid carcinoma: comparison with ultrasound and contrast-enhanced CT. *Clin Endocrinol* (2006) 65(3):402–7. doi: 10.1111/j.1365-2265.2006.02612.x
38. Kim E, Park JS, Son K-R, Kim J-H, Jeon SJ, Na DG. Association: Preoperative diagnosis of cervical metastatic lymph nodes in papillary thyroid carcinoma: comparison of ultrasound, computed tomography, and combined ultrasound with computed tomography. *Thyroid* (2008) 18(4):411–8. doi: 10.1089/thy.2007.0269
39. Zhou Y-L, Gao E-L, Zhang W, Yang H, Guo G-L, Zhang X-H, et al. Factors predictive of papillary thyroid micro-carcinoma with bilateral involvement and central lymph node metastasis: a retrospective study. *World J Surg Oncol* (2012) 10:67. doi: 10.1186/1477-7819-10-67
40. Eun MO, Yoo SC, Won JS, Young DL. The pattern and significance of the calcifications of papillary thyroid microcarcinoma presented in preoperative neck ultrasonography. *Ann Surg Treat Res* (2014) 86(3):115–21. doi: 10.4174/astr.2014.86.3.115
41. Wei X, Li D, Gao M, Zhang S, Wang M, Wang X, et al. Prediction of cervical lymph node metastases in papillary thyroid microcarcinoma by sonographic features of the primary site. *Cancer Biol Med* (2019) 16(3):587–94. doi: 10.20892/j.issn.2095-3941.2018.0310
42. Johannessen JV, Sobrinho-Simões M. The origin and significance of thyroid psammoma bodies. *Lab Invest* (1980) 43(3):287–96. doi: 10.1136/jcp.2004.023572

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 25 February 2021
doi: 10.3389/fendo.2020.588024

# Long-Term Outcomes and Prognoses of Elderly Patients (≥65-Years-Old) With Distant Metastases From Well-Differentiated Thyroid Cancer During Radioiodine Therapy and Follow-Up

*Zhong-Ling Qiu, Chen-Tian Shen, Zhen-Kui Sun, Hong-Jun Song, Chuang Xi, Guo-Qiang Zhang, Yang Wang* and Quan-Yong Luo**

*Department of Nuclear Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China*

OPEN ACCESS

**Edited by:**
*Christoph Reiners, University Hospital Würzburg, Germany*

**Reviewed by:**
*Masami Murakami, Gunma University, Japan*
*Silvia Martina Ferrari, University of Pisa, Italy*

***Correspondence:**
*Quan-Yong Luo*
*lqyn@sh163.net*
*Yang Wang*
*hongchayang@sina.com*

**Specialty section:**
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

**Received:** *28 July 2020*
**Accepted:** *16 November 2020*
**Published:** *25 February 2021*

**Citation:**
*Qiu Z-L, Shen C-T, Sun Z-K, Song H-J, Xi C, Zhang G-Q, Wang Y and Luo Q-Y (2021) Long-Term Outcomes and Prognoses of Elderly Patients (≥65-Years-Old) With Distant Metastases From Well-Differentiated Thyroid Cancer During Radioiodine Therapy and Follow-Up. Front. Endocrinol. 11:588024. doi: 10.3389/fendo.2020.588024*

**Objective:** The objective of this study was to investigate the clinicopathological characteristics, long-term outcomes, and prognostic factors of elderly patients with distant metastases at initial diagnosis from well-differentiated thyroid cancer (WDTC) during radioactive iodine ($^{131}$I) treatment and follow-up.

**Methods:** A retrospective review of medical records identified 183 elderly patients with DTC who underwent $^{131}$I treatment at our institution between 2006 and 2019.

**Results:** In total, 57 elderly WDTC patients with distant metastases were enrolled in this study. After $^{131}$I treatment, 32 (56.14%) patients had $^{131}$I avidity and 25 (43.86%) had non-$^{131}$I avidity; 35 (61.40%) cases were classified as radioiodine refractory (RR)-WDTC and 22 (38.60%) as non-RR-WDTC. At the end of follow-up, 25 (43.86%) patients had died and 32 (56.14%) were alive. The 5- and 10-year overall survival (OS) rates were 71.50% and 30.49%, respectively, while the 5- and 10-year disease-specific survival (DSS) rates were 76.89% and 48.71%, respectively. Multivariate analyses showed that gross extrathyroidal extension and RR-DTC were independent prognostic factors for poor OS (P=0.04 and P=0.03, respectively), while gross extrathyroidal extension, extrapulmonary distant metastases, and RR-WDTC were independent prognostic factors for poor DSS at the end of follow-up (P=0.02, P=0.03, and P=0.02, respectively).

**Conclusions:** WDTC with distant metastases at initial diagnosis accounted for 31.15% of all elderly patients with DTC. Gross extrathyroidal extension and RR-DTC were the major factors associated with poor OS; gross extrathyroidal extension, extrapulmonary distant metastases, and RR-DTC were independent prognostic factors for poor DSS in elderly DTC patients with distant metastases.

**Keywords: distant metastases, radioiodine therapy, elderly patients, well-differentiated thyroid cancer, follow-up**

## INTRODUCTION

Over the past two decades, differentiated thyroid cancer (DTC) has become the most common endocrine malignancy with the fastest growth rate worldwide (1). Despite its rising incidence, it has an excellent prognosis, and the vast majority of patients sustain long-term survival, with the 10-year overall survival (OS) rate currently >90% after total or near-total thyroidectomy combined with radioiodine ($^{131}$I) ablation therapy (2). Previous studies have shown that age at initial diagnosis of DTC is the factor most associated with recurrence, survival, and prognosis (3). Elderly patients have a poorer prognosis and more aggressive DTC, which is characterized by larger tumors, extrathyroidal invasion, and distant metastasis (4). Although the AJCC/UICC revised the age cut-off from 45- to 55-years-old in the latest TNM staging system (2016), elderly DTC patients continue to have significantly decreased survival compared with younger patients (5). Regarding the optimal cut-off value for defining "the elderly" DTC population, 60, 65, and 70 years have been reported in different studies (6, 7). According to the World Health Organization, most developed countries have adopted the definition of ≥65 years as "the elderly".

It has been reported that the prevalence of distant metastasis is relatively rare in DTC, with previous reports varying from 4% to 23% (8, 9). Lung and bone are the most common distant metastatic sites, and other less common organs include brain, kidney, skin, muscle, and pleura (10). For nearly eighty years, $^{131}$I has been the main treatment for distant DTC metastases after thyroidectomy. For radioiodine-refractory (RR)-DTC with distant metastases, clinical trials have demonstrated that molecular targeted drugs have good therapeutic efficacy, advancing the prospects for these patients. Now, sorafenib and lenvatinib are recommended as the first-line therapy for progressive RR-DTC according to the latest ATA management guidelines (11–13). It has been reported that several independent prognostic factors are related to the poor prognosis of DTC patients with distant metastases, such as age at initial diagnosis of distant metastases, loss of $^{131}$I avidity for distant metastases, presence of extrapulmonary distant metastases, and patients who initially present with distant metastases (8, 9, 14, 15).

Although the incidence of distant metastases in elderly DTC patients has significantly increased (4); to the best of our knowledge, there is little published information on the long-term outcomes of elderly well-DTC (WDTC) patients with distant metastases. To address this issue and raise awareness of this disease, this study reviewed the experience of a single tertiary medical center in China with a relatively large series of elderly (≥65 years) WDTC patients who presented with distant metastases at initial diagnosis. We analyzed the clinicopathological characteristics, long-term outcomes, and independent prognostic factors for overall survival (OS) and distant metastatic disease-specific survival (DSS) in these elderly patients with distant metastases.

## MATERIALS AND METHODS

### Eligible Patients

We retrospectively reviewed the medical records of 11,984 consecutive DTC patients treated with $^{131}$I after total or near-total thyroidectomy between 2006 and 2019 at Shanghai Sixth People's Hospital, a major $^{131}$I treatment center in China. In total, 57 elderly WDTC patients were enrolled in this study (**Figure 1**). This study was approved by the Institutional Review Board of the Shanghai Sixth People's Hospital.

### Baseline Variables

Demographics, clinicopathological characteristics, $^{131}$I treatment results, and follow-up data for all eligible patients are shown in **Table 1**. Age was determined at the time of initial diagnosis of distant metastases from WDTC. Pathological type only included classic PTC and follicular thyroid cancer (FTC). Follicular variant of PTC (FV-PTC) and Hürthle cell cancer were classified into the PTC and FTC subtypes, respectively. Poor-DTC and aggressive subtypes of PTC were excluded. Extrathyroidal extension was divided into three categories: "No," "Minimal," and "Gross" according the 2015 ATA guidelines (11). "Minimal" was defined as microscopic tumor invasion into the perithyroidal soft tissues, while "Gross" was defined as macroscopic tumor invasion into perithyroidal soft tissues. N stage was evaluated based on the eighth edition of the AJCC/TNM cancer staging system (16). According to a past report, distant metastases confirmed within 1 year from the initial thyroid surgery were considered distant metastases at initial presentation, while distant metastases detected >1 year after initial diagnosis were considered delayed distant metastases (15).

### Diagnosing Distant Metastases From WDTC

Diagnoses of distant metastases from WDTC were established and confirmed by at least one of the following criteria, which was similar to our previous study (17, 18). Criterion I: distant metastases were found or detected according to clinical manifestations and comprehensive imaging such as computed tomography (CT), magnetic resonance imaging (MRI), and/or $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG-PET/CT), and pathological results from operations or biopsies that confirmed the lesions originated from thyroid tissue; Criterion II: $^{131}$I uptake of distant metastatic lesions was found on therapeutic $^{131}$I whole body scan ($^{131}$I-WBS), with the distant metastases detected on at least one imaging modality, including $^{131}$I-single-photon emission computed tomography/computed tomography ($^{131}$I-SPECT/CT), CT, and/or MRI; and Criterion III: even if therapeutic $^{131}$I-WBS did not show positive lesions but the DTC patients had elevated thyroglobulin (Tg) or progressively increased thyroglobulin antibody (TgAb) levels, the distant metastases could be found on $^{18}$F-FDG-PET/CT scans.

### $^{131}$I Treatment of Distant Metastases

To implement $^{131}$I treatment after total or near-total thyroidectomy, all DTC patients consumed a low-iodine diet and were withdrawn from levothyroxine therapy for at least two weeks to achieve thyroid stimulating hormone (TSH) levels of ≥30 mIU/L, according to the ATA guideline (11). All patients were subjected to routine measurements of TSH, free triiodothyronine (FT3), free thyroxine (FT4), Tg, and TgAb, neck ultrasonography (US), CT, and/or MRI

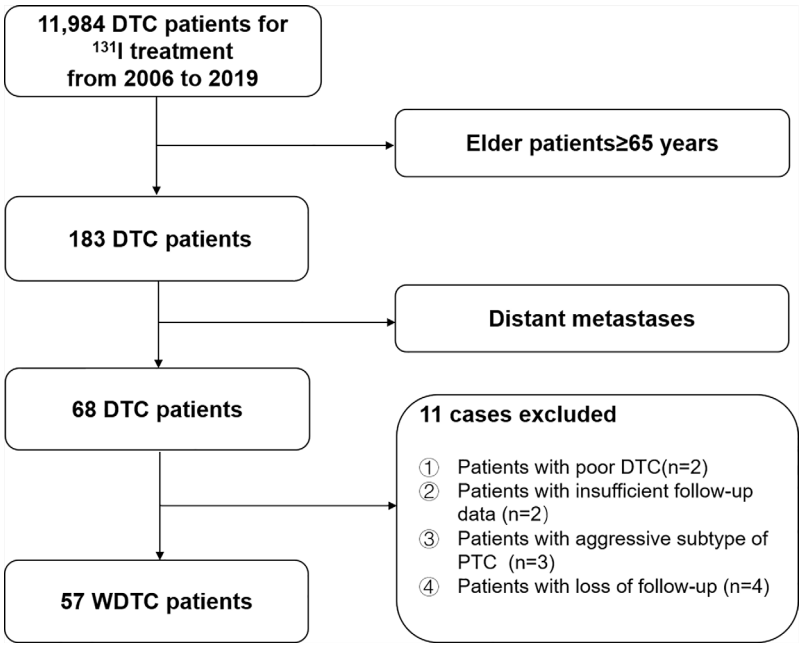


**FIGURE 1** | Flow diagram of the selection process for elderly (≥65-years-old) well-differentiated thyroid cancer (WDTC) patients with distant metastases at initial diagnosis.

scans prior to $^{131}$I treatment. Next, if distant metastasis were diagnosed before $^{131}$I treatment, patients received an oral dose of $^{131}$I with standard activity of 5.55–7.40 GBq (150–200 mCi) to ablate remnant thyroid disease and treat distant metastases. If distant metastases were diagnosed on the $^{131}$I-WBS and another imaging modality after the first $^{131}$I therapy, 3.7 GBq (100 mCi) was used for the initial treatment to ablate remnant thyroid disease, and then 5.55–7.40 GBq (150–200 mCi) was taken orally for subsequent treatments aimed at treating distant metastases. The intervals for repeated $^{131}$I treatments were 4–12 months. Subsequent $^{131}$I treatments were interrupted in patients with weakly $^{131}$I-avid or non-$^{131}$I-avid distant metastases on therapeutic $^{131}$I-WBS.

## Evaluating RR-DTC

We evaluated RR-DTC according to the 2015 ATA management guidelines, which defined structurally evident RR-DTC depending on the following criteria: (1) the primary and/or metastatic lesions do not absorb $^{131}$I on $^{131}$I-WBS; (2) the primary and/or metastatic lesions lose the ability to concentrate $^{131}$I after previously being $^{131}$I-avid lesions; (3) $^{131}$I is heterogeneously concentrated into some lesions on $^{131}$I-WBS but not others; and (4) primary and/or metastatic lesions show progressive disease (PD) within 1 year following $^{131}$I treatment despite sustained concentration of $^{131}$I. The therapeutic effect of $^{131}$I was divided into two categories: PD and non-PD. Similar to our previous report (15), PD responses were evaluated by the Response Evaluation Criteria in Solid Tumors Guideline Version 1.1 (RECIST1.1) (19) for pulmonary metastases and the MDA criteria (20) for bone metastases. For pulmonary metastases from DTC, PD was defined as at least a 20% increase in the sum of diameters for all measured target lesions with an absolute increase of at least 5 mm in the sum of diameters and/or the appearance of new lesions, while for bone metastases from DTC, PD was defined as at least a 25% increase in the size of measurable lesions using CT or MRI, at least a 25% subjective increase in the size of ill-defined lesions using CT or MRI, and/or the appearance of new lesions.

## Other Treatments for Elderly Patients With Distant Metastases

For RR-DTC, molecular targeted therapies, such as tyrosine kinase inhibitors (TKIs), have emerged as new treatment modalities (21, 22). The ATA guidelines recommend sorafenib and lenvatinib for the treatment of progressive RR-DTC (11–13). Since September 2017, only sorafenib has been approved as a first-line drug for progressive RR-DTC in China. In this study, sorafenib was used to treat progressive RR-DTC with distant metastases in eight patients. Other treatment modalities for distant metastases include external radiotherapy, palliative surgery, chemotherapy, bisphosphonates, and interventional therapy (11). In addition to $^{131}$I therapy, palliative surgery was performed in four patients, and seven patients underwent external radiotherapy during $^{131}$I treatment and follow-up. No other therapies were performed on the elderly patients with distant metastases in this study.

## Follow-Up Strategy

After $^{131}$I treatment, routine follow-up was performed for every patient, and the follow-up period for this study was until the end of June 2019. During the follow-up period, FT3,

**TABLE 1** | Patient characteristics of well-differentiated thyroid cancer (WDTC) with distant metastases.

| | N (%) or Value |
|---|---|
| **Age at initial diagnosis of distant metastases (years) (Mean±SD, Median, Range)** | 69.84±5.01,68,65–86 |
| 65–70 | 34(59.65%) |
| ≥70 | 23(40.35%) |
| **Gender** | |
| Male | 24(42.11%) |
| Female | 33(57.89%) |
| **Number of thyroid surgeries** | |
| 1 | 46(80.70%) |
| >1 | 11(19.30%) |
| **Pathological type** | |
| PTC | 46(80.70%) |
| FTC | 11(19.30%) |
| **Maximal primary tumor size (cm) (Mean ± SD, Median, Range)** | 3.30±1.74,3.2,0.4–10.2 |
| <2 | 10(17.54%) |
| 2–4 | 34(59.65%) |
| ≥4 | 13(22.81%) |
| **Tumor multifocality** | |
| No | 36(63.16%) |
| Yes | 21(36.84%) |
| **Extrathyroidal extension** | |
| No | 33(57.90%) |
| Minimal | 9(15.79%) |
| Gross | 15(26.31%) |
| **N stage** | |
| N0 | 13(22.81%) |
| N1a | 25(43.86%) |
| N1b | 19(33.33%) |
| **Local persistence or recurrence during $^{131}$I treatment and follow-up** | |
| No | 37(64.91%) |
| Yes | 20(35.09%) |
| **Timing of distant metastasis** | |
| At initial presentation | 12(21.05%) |
| Delayed distant metastases | 45(78.95%) |
| **Symptom of distant metastases at initial diagnosis** | |
| Asymptomatic | 30(52.63%) |
| Symptomatic | 27(47.37%) |
| **Site of distant metastases at initial diagnosis** | |
| Lung only | 33(57.89%) |
| Bone only | 8(14.04%) |
| ≥2 Organ system | 16(28.07%) |
| **Treatment modalities of distant metastases** | |
| $^{131}$I treatment | 57(100.00%) |
| Palliative surgical treatment | 4(0.07%) |
| External radiotherapy | 7(12.28%) |
| TKIs therapy | 8(14.04%) |
| **$^{131}$I avidity** | |
| Yes | 32(56.14%) |
| No | 25(43.86%) |
| **RR-DTC** | |
| No | 22(38.60%) |
| Yes | 35(61.40%) |
| **Preablation stimulated Tg (ng/mL)(Mean±SD, Median, Range)** | 498.32 ±11124.39,430.3,0.05–49320 |
| **$^{131}$I Cumulative administered(Mean±SD, Median, Range)** | 15.58 ±14.94,11.10,3.7–72.5 |
| **Number of courses for $^{131}$I therapy (Mean±SD, Median, Range)** | 2.75±2.34,2.0,1–12 |

FT4, TSH, Tg, and TgAb levels were measured and physical examination and US of the neck were performed every 3–6 months, chest CT was performed annually to compare changes in the pulmonary metastatic lesions with previous results. For bone metastases, at least one imaging examination (CT, MRI, or $^{18}$F-FDG-PET/CT) was conducted annually to evaluate the clinical course of metastatic lesions and confirm PD. At the end of follow-up, the OS of these patients was calculated according to the time from initial detection of distant metastatic lesions to end of follow-up or death from any cause, while DSS was calculated from the time of initially detecting distant metastatic lesions to the end of follow-up or death from the distant metastatic disease.

## Statistical Analysis

All statistical analyses were performed using GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA) and MedCalc version 17.0 (MedCalc Software, Mariakerke, Belgium). Continuous variables are presented as median and means ± standard deviations with range. Categorical variables were expressed as exact numbers with proportions. OS and DSS survival curves were analyzed by Kaplan–Meier method from the initial diagnosis of distant metastasis to the end of follow-up or death. To evaluate prognostic factors for OS and DSS at the end of follow-up, univariate analysis was performed using the Log-rank test, and then multivariate analysis was calculated using the Cox proportional hazard model. A p-value <0.05 was considered significant. Parameters with P-values <0.1 that displayed significant influence on the OS and DSS rates of elderly WDTC patients with distant metastases in univariate analyses were included in multivariate analyses. In contrast, parameters with P-values ≥0.1 were not included in multivariate analyses.

# RESULTS

## Patient Demographics

Between 2006 and 2019, 183 elderly patients (≥65-years-old) with DTC were treated with $^{131}$I after total or near-total thyroidectomy in our department. Among them, 57 (31.15%) elderly WDTC patients with distant metastases were confirmed according to the inclusion criteria. Baseline clinicopathological features of these elderly WDTC patients with distant metastases are shown in **Table 1**.

## Diagnoses and Clinical Symptoms of Distant Metastasis

According to the diagnostic criteria for distant metastases in elderly WDTC patients, 13 cases (22.81%) were diagnosed according to Criterion I, 29 (50.88%) were diagnosed by Criterion II, and 15 (26.32%) were detected by Criterion III. Among the cases detected by Criterion III, three were negative for Tg and had persistently elevated TgAb levels, while the remaining 12 cases with positive Tg levels were included. In this study, 27 (47.37%) patients were symptomatic and

30 (52.63%) lacked any clinical symptoms upon the initial diagnosis of distant metastases. Among the 27 patients with clinical symptoms, 15 suffered from cough and expectoration, fiver had hemoptysis, six suffered from shortness of breath and/or breathing difficulties, three cases had pleural effusion, nine hade bone pain, two had pathologic fractures, and one patient had spinal cord compression.

## The Distribution of Initial Distant Metastases

Among the 57 elderly DTC patients with distant metastases, 33 (57.89%) were found to have lung metastases alone, eight (14.04%) presented with only bone metastases, and 16 (28.07%) had at least two synchronous distant organ metastases including 10 with synchronous bone and lung metastases, two with synchronous lung and brain metastases, two with synchronous lung and renal metastases, one with synchronous bone and brain metastases, and one with synchronous bone, lung and renal metastases (**Table 1**). Among the 48 cases with lung metastases, 17 were classified as micro-metastases (<1 cm) and 31 as macro-metastases (≥1 cm) according the largest size of the lung lesions. For the 20 patients with bone metastases, 16 had multiple bone metastases and four had a single bone metastasis.

## Response to $^{131}$I Therapy

The responses to $^{131}$I treatment are showed in **Table 1**. $^{131}$I-WBS showed that 32 elderly patients (56.14%) could concentrate $^{131}$I, while 25 (43.86%) did not show therapeutic $^{131}$I concentration ability. According to the evaluation criteria for RR-DTC, 35 cases (61.40%) were classified as RR-WDTC and 22 (38.60%) as non-RR-WDTC. Among the 35 RR-DTC cases, 25 (43.84%) were identified by criterion 1, three (5.36%) by criterion 2, two (3.51%) by criterion 3, and five (8.77%) by criterion 4 (**Figure 2A**). According to the evaluation criteria of PD during $^{131}$I treatment, 40 patients (71.18%) did not show PD, while 17 (29.82%) had PD, including 12 who were classified by criterion 1, one by criterion 2, and five by criterion 4.

## Clinical Outcomes

At the end of follow-up, 25 patients (43.86%) had died and 32 (56.14%) were alive. Among those who had died, 19 (33.33%) were caused by distant metastatic disease, including 10 from lung metastases, six from bone metastases, two from brain metastases, and one from renal metastasis; five (8.77%) deaths were caused by other causes, including one patient from heart failure, one from colorectal cancer, one from lung infection, two from cerebrovascular diseases, and one (1.76%) from locally invasive WDTC (**Figure 2B**). The median survival after the initial diagnosis of distant metastasis was 7.3 years (range: 0.1–13.3 years). The OS rate was 18.29% at the last follow-up, with 5- and 10-year OS rates of 71.50% and 30.49%, respectively (**Figure 3A**). The DSS rate was 29.23% at the last follow-up, with 5- and 10-year DSS rates of 76.89% and 48.71%, respectively (**Figure 3B**).

## Prognostic Factors for OS

The univariate analysis of prognostic factors for elderly DTC patients with distant metastases at the last follow-up is shown in **Table 2**. Four factors were found to be associated with OS, including pathological type, extrathyroidal extension, site of distant metastases at initial diagnosis, and RR-DTC status. Patient stratification showed that the median OS values of elderly patients with DTC who had gross extrathyroidal extension, extrapulmonary distant metastases, and RR-DTC were significantly lower than those of patients with FTC, no or minimal extrathyroidal extension, pulmonary only or no distant metastases, and non-RR-DTC (P=0.04, P=0.02, P=0.03, and P=0.02, respectively) (**Figure 4**). However, no significant differences were observed in OS for the other factors (P>0.05) (**Table 2**). Multivariate analyses that included

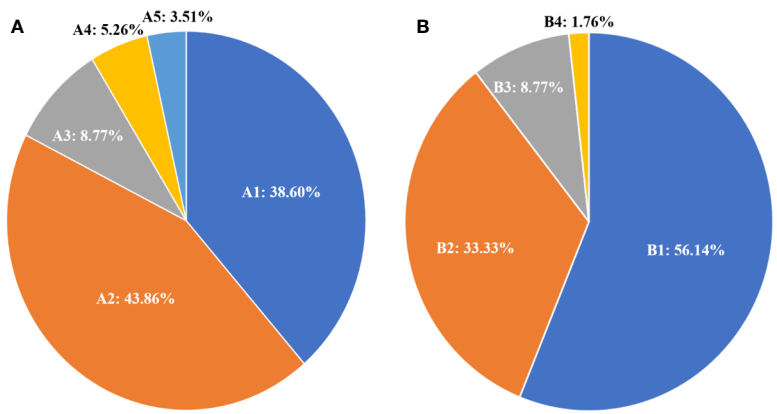


**FIGURE 2** | Distribution and percentage of $^{131}$I treatment status according to the RR-DTC evaluation criteria **(A)**; A1: non-RR-WDTC; A2: identified by Criterion I; A3: by Criterion IV; A4: by Criterion II; and A5: by Criterion III. Distribution and percentage of causes of death for these patients **(B)**; B1: patients alive at the last follow-up; B2: patients who died of distant metastases; B3: patients who died of other reasons; B4: the patient who died of locally invasive disease.

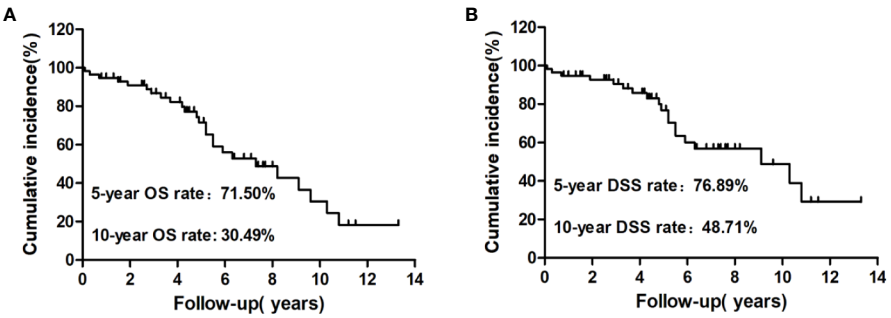


**FIGURE 3** | Kaplan–Meier analysis of cumulative overall survival (OS) **(A)** and disease-specific survival (DSS) **(B)** rates from the initial diagnosis of distant metastasis to the end of follow-up for these patients.

five factors (P<0.1) from the univariate analysis indicated that gross extrathyroidal extension (hazard ratio [HR]: 3.07, 95% confidence interval [CI]: 1.413–9.382, P=0.04) and RR-DTC (HR: 2.36, 95% CI: 1.029–6.314, P=0.03) were independent factors associated with poor prognosis (**Table 3**). The other three factors from the univariate analysis (pathological type, N stage, and site of distant metastases) were not independent prognostic factors for OS (P>0.05) (**Table 3**).

## Prognostic Factors for DSS

Factors predictive of DSS were determined by univariate analysis using the log-rank test (**Table 4**). Univariate analysis demonstrated that extrathyroidal extension, symptoms of distant metastases, site of distant metastases at initial diagnosis, and RR-DTC status were associated with DSS in these patients. Patients without or with minimal extrathyroidal extension, without symptoms of distant metastases, with only pulmonary metastases, and without RR-DTC had better median DSS rates those with gross extrathyroidal extension, symptomatic distant metastases, extrapulmonary distant metastases, and RR-DTC (P=0.01, P=0.02, P=0.02, and P=0.01, respectively) (**Figure 5**). Multivariate analysis that included four factors (P<0.1) from the univariate analysis showed that gross extrathyroidal extension (HR: 4.94, 95% CI: 1.511–17.319, P=0.02), extrapulmonary distant metastases (HR: 2.48, 95% CI: 1.030–9.001, P=0.03), and RR-DTC (HR: 2.89, 95% CI: 1.378–9.017, P=0.02) were independent prognostic factors related to poor DSS. There was no significant association between DSS and the presence of symptomatic distant metastases (P=0.05) (**Table 5**).

# DISCUSSION

Although the prevalence of distant metastasis from DTC in elderly patients has been increasing, there have been few reports about the incidence, clinicopathological features, long-term outcomes, and prognostic factors of patients over 65-years-old with distant metastases from WDTC. To the best of our knowledge, only Han et al. (23) have described this patient population, finding that 17 of 86 elderly patients (>65-years-old) experienced distant metastases from DTC between 1994 and 2012, with an incidence rate of 19.77%. In this study, we retrospectively found that 57 of 183 elderly WDTC patients had distant metastases, an incidence rate of 31.15%, which represents a relatively large series of elderly patients with distant metastases who were treated with $^{131}$I at a single center. Most studies have shown that distant metastases occurred in 4%–23% of DTC patients (8, 14, 24, 25), which was lower than the results of our study. Our data support the conclusion that elderly DTC patients are more prone to having distant metastases.

In previous studies, the 5-year OS rates of DTC patients with distant metastases ranged from 42% to 88% and the 10-year OS rates ranged from 25% to 77% (8, 24–34); the 5-year DSS rates of DTC patients with distant metastases have ranged from 57.9% to 80% and the 10-year DSS rates have ranged from 26% to 48.3% (27, 30, 33, 34). In our study, the 5- and 10-year OS rates were 71.50% and 30.49%, respectively, while the 5- and 10-year DSS rates were 76.89% and 48.71%, respectively. All of these studies, including ours, have found heterogeneous clinical outcomes and a wide range of mortality risks for DTC patients with distant metastases, which may be caused by different sample sizes, diagnostic criteria, inclusion and/or exclusion criteria, and treatment modes. For instance, our inclusion criteria only included the well-differentiated pathological type among all DTC patients ≥65 years with metastatic disease. Regarding DTC patients with distant metastases, previous studies have demonstrated several independent prognostic factors associated with poor prognosis, including age at initial diagnosis of distant metastases, $^{131}$I avidity, timing of distant metastases, pathological type, and presence of extrapulmonary distant metastases (8, 9, 14, 15). Because of the inconsistencies in these previous studies regarding OS and DSS, we thought it valuable to assess the prognostic factors in our cohort of elderly DTC patients with distant metastases. Our multivariate analysis revealed that gross extrathyroidal extension and RR-DTC were independent factors associated with poor OS, while gross extrathyroidal extension, extrapulmonary distant metastases, and RR-DTC were independent prognostic factors related to poor DSS in elderly WDTC patients with distant metastases.

The most common pathological types of of DTC include PTC and FTC. Previous studies have showed the different ratios

**TABLE 2 |** Univariate analysis showed the influence of prognostic factors on the overall survival (OS) of the elderly well-differentiated thyroid cancer (WDTC) patients with distant metastases by using the Log-rank test at the end of follow-up.

| Variable | No. of patients | No. of deaths (%) | Log-rank | Hazard ratio | 95 % CI | P value |
|---|---|---|---|---|---|---|
| **Age at initial diagnosis of distant metastases (years)** | | | **2.43** | | | **0.12** |
| 65–70 | 34 | 10 (29.41%) | | 1 | | |
| ≥70 | 23 | 15 (65.22%) | | 1.67 | 0.742–3.760 | |
| **Gender** | | | **1.46** | | | **0.23** |
| Male | 24 | 8 (33.33%) | | 1 | | |
| Female | 33 | 17 (51.52%) | | 1.63 | 0.738–3.615 | |
| **Number of thyroid surgeries** | | | **0.07** | | | **0.80** |
| 1 | 46 | 21(45.65%) | | 1 | | |
| >1 | 11 | 4 (36.36%) | | 0.88 | 0.313–2.447 | |
| **Pathological type** | | | **4.13** | | | **0.04** |
| FTC | 11 | 3(27.27%) | | 1 | | |
| PTC | 46 | 22(47.83%) | | 2.61 | 1.035–6.556 | |
| **Maximal primary tumor size** | | | **0.19** | | | **0.91** |
| <2 | 10 | 2(20.00%) | | 1 | | |
| 2–4 | 34 | 15(44.12%) | | 1.17 | 0.282–4.894 | |
| ≥4 | 13 | 8(61.52%) | | 1.51 | 0.345–6.630 | |
| **Tumor multifocality** | | | **0.64** | | | **0.43** |
| No | 36 | 15(41.67%) | | 1 | | |
| Yes | 21 | 10(47.62%) | | 1.12 | 0.500–2.495 | |
| **Extrathyroidal extension** | | | **7.60** | | | **0.02** |
| No | 26 | 5(19.23%) | | 1 | | |
| Minimal | 12 | 7(58.33%) | | 2.13 | 0.654–6.952 | |
| Gross | 19 | 13(68.42%) | | 3.88 | 1.500–10.04 | |
| **N stage** | | | **5.76** | | | **0.06** |
| N0 | 13 | 3 (23.08%) | | 1 | | |
| N1a | 25 | 13 (52.00%) | | 2.470 | 0.753–8.070 | |
| N1b | 19 | 9 (43.37%) | | 4.405 | 1.508–12.860 | |
| **Local persistence or recurrence** | | | **0.63** | | | **0.43** |
| No | 37 | 16(43.24%) | | 1 | | |
| Yes | 20 | 9(45.00%) | | 1.43 | 0.592–3.460 | |
| **Timing of distant metastasis** | | | **0.64** | | | **0.42** |
| At initial presentation | 12 | 5 (41.67%) | | 1 | | |
| Delayed distant metastases | 45 | 20 (44.44%) | | 1.444 | 0.588–3.548 | |
| **Symptom of distant metastases** | | | **1.70** | | | **0.19** |
| Asymptomatic | 30 | 14 (46.67%) | | 1 | | |
| Symptomatic | 27 | 11 (40.74%) | | 0.56 | 0.237–1.336 | |
| **Site of distant metastases at initial diagnosis** | | | **4.85** | | | **0.03** |
| Pulmonary only | 33 | 10 (30.30%) | | 1 | | |
| Extrapulmonary | 24 | 15 (62.50%) | | 2.486 | 1.105–5.594 | |
| **Treatment modalities of distant metastases** | | | **0.004** | | | **0.95** |
| RAI treatment | 40 | 17 (42.50%) | | 1 | | |
| RAI combined with other treatment | 17 | 8 (47.06%) | | 1.378 | 0.605–3.136 | |
| **$^{131}$I avidity** | | | **0.32** | | | **0.57** |
| Yes | 32 | 14 (43.75%) | | 1 | | |
| No | 25 | 11 (44.00%) | | 1.267 | 0.561–2.859 | |
| **RR-DTC** | | | **5.16** | | | **0.02** |
| No | 22 | 4 (18.18%) | | 1 | | |
| Yes | 35 | 21 (60.00%) | | 2.57 | 1.138–5.800 | |

between PTC and FTC of DTC patients with distant metastases, with ratios varying from 4:1 to 1:1 (8, 24–34). However, our study found a significantly higher ratio than any previous study, with a PTC to FTC ratio of 4.18:1. This difference may be due to the different pathological subtypes included in PTC and FTC. In our study, PTC consisted of classical PTC and its subtype FVPTC, while FTC comprised classical FTC and its subtype Hürthle cell cancer. Most previous studies have also found no significant differences in the prognoses of DTC patients with distant metastases between the PTC and FTC subgroups, which was in accordance with our findings (8, 14, 24–26, 28, 29, 31, 32). Although our study found that FTC had a better OS than PTC by univariate analysis, there was not a significant difference in OS between PTC and FTC by multivariate analysis.

Distant metastases from DTC are usually located in the lungs and/or bones. The sites of distant metastases can be divided into three categories: lung only, bone only, and lung and/or bone with or without other distant metastases (≥2 organ systems). All previous studies have found that lung-only metastasis accounted for the largest proportion of all distant metastases, with rates varying from 43% to 66%; these data are in concordance with our study (57.89%) (8, 24, 26–34). Most studies have found that the

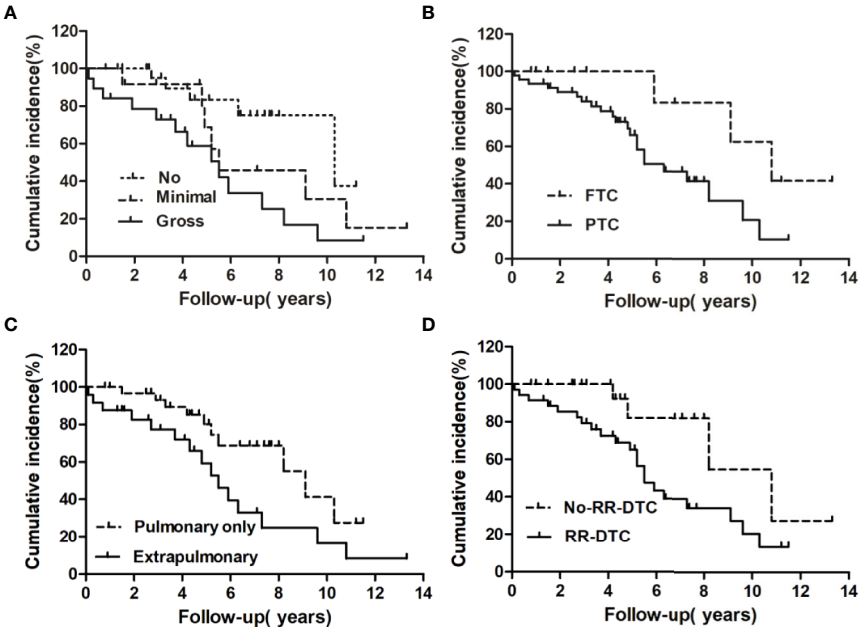


**FIGURE 4** | Univariate analysis of the prognostic factors for median overall survival (OS) at the end of follow-up; the median OS of patients differed significantly according to extrathyroidal extension **(A)**, pathological type **(B)**, site of distant metastases at initial diagnosis **(C)**, and RR-DTC status **(D)**.

proportion of patients with bone-only metastases was significantly higher than that of patients with ≥2 distant organ system metastases (14, 24, 26, 28, 34). In contrast, a few studies have indicated that the proportion of cases with ≥2 organ system metastases was significantly higher than that of bone-only metastases cases (30, 32), which is what we found in this study (28.07% vs. 14.4%). This finding may be due to the fact that elderly patients are more likely to have multiple distant metastases. Most previous studies have found that patients with lung or bone metastases only had better survival outcomes than patients with synchronous bone and lung metastases (10, 17). However, in this study, the numbers of patients with bone-only metastases were relatively small, so this could have been caused by statistical deviation. Thus, we divided our patients into two groups: those with pulmonary-only and extrapulmonary distant metastases. Univariate analysis showed that there were significant differences between the two groups in OS, but multivariate analysis revealed that pulmonary-only metastasis was not an independent factor associated with poor OS. These differences may have been caused by the six patients who died from other causes, which may have led to biases. For example, univariate and multivariate analysis for DSS demonstrated that site of metastasis was a significant prognostic factor in these patients.

**TABLE 3** | Multivariate analysis of prognostic factors for the overall survival (OS) of the elderly differentiated thyroid cancer (DTC) patients presenting with distant metastasis according to Cox's Proportional Hazards Model at the end of follow-up.

| Variable | No. of patients | Hazard ratio | 95 % CI | P value |
|---|---|---|---|---|
| **Pathological type** | | | | |
| FTC | 11 | 1 | | |
| PTC | 46 | 1.98 | 0.925–5.832 | 0.08 |
| **Extrathyroidal extension** | | | | |
| No | 26 | 1 | | |
| Minimal | 12 | 1.86 | 0.472–4.853 | 0.32 |
| Gross | 19 | 3.07 | 1.413–9.382 | 0.04 |
| **N stage** | | | | |
| N0 | 13 | 1 | | |
| N1a | 25 | 1.320 | 0.553–4.162 | 0.27 |
| N1b | 19 | 1.871 | 0.708–10.354 | 0.22 |
| **Site of distant metastases at initial diagnosis** | | | | 0.06 |
| Pulmonary only | 33 | 1 | | |
| Extrapulmonary | 24 | 2.032 | 0.792–6.057 | |
| **RR-DTC** | | | | |
| No | 22 | 1 | | |
| Yes | 35 | 2.36 | 1.029–6.314 | 0.03 |

A previous meta-analysis demonstrated that gross extrathyroidal extension is a major predictive factor for distant metastases from DTC, with a prevalence rate in DTC patients with gross extrathyroidal extension of 14.3% compared with only 3.8% in DTC patients without gross extrathyroidal extension (35). However, it is unclear if gross extrathyroidal extension is a major prognostic factor for DTC patients with distant metastases because extrathyroidal extension has not been included as a variable for univariate or multivariate analyses in most previous studies (8, 14, 24, 26–28, 30–34). Additionally, the study by Hirsch et al. revealed that gross extrathyroidal extension was not associated with improved OS or disease progression in DTC (including PTC and FTC) patients with distant metastases (9). In another study, gross extrathyroidal extension was found to be associated with decreased

**TABLE 4 |** Univariate analysis showed the influence of prognostic factors on the disease-specific survival (DSS) of the elderly well-differentiated thyroid cancer (WDTC) patients with distant metastases by using the Log-rank test at the end of follow-up.

| Variable | No. of patients | No. of deaths (%) | Log-rank | Hazard ratio | 95 % CI | P value |
|---|---|---|---|---|---|---|
| **Age at initial diagnosis of distant metastases (years)** | | | **1.12** | | | **0.29** |
| 65–70 | 34 | 8 (23.53%) | | 1 | | |
| ≥70 | 23 | 11 (47.83%) | | 1.65 | 0.653–4.173 | |
| **Gender** | | | **1.30** | | | **0.25** |
| Male | 24 | 6(25.00%) | | 1 | | |
| Female | 33 | 13(39.39%) | | 1.699 | 0.683–4.223 | |
| **Number of thyroid surgeries** | | | **0.07** | | | **0.79** |
| 1 | 46 | 16(34.78%) | | 1 | | |
| >1 | 11 | 3(27.27%) | | 0.85 | 0.263–2.774 | |
| **Pathological type** | | | **1.85** | | | **0.17** |
| FTC | 11 | 3(27.27%) | | 1 | | |
| PTC | 46 | 16(34.78%) | | 2.08 | 0.721–6.098 | |
| **Maximal primary tumor size** | | | **0.11** | | | **0.95** |
| <2 | 10 | 2(20.00%) | | 1 | | |
| 2–4 | 34 | 11(32.35%) | | 1.16 | 0.229–5.848 | |
| ≥4 | 13 | 6(46.15%) | | 0.77 | 0.159–3.759 | |
| **Tumor multifocality** | | | **0.17** | | | **0.68** |
| No | 36 | 10(27.78%) | | 1 | | |
| Yes | 21 | 9(42.86%) | | 1.121 | 0.481–3.048 | |
| **Extrathyroidal extension** | | | **8.86** | | | **0.01** |
| No | 26 | 3(11.54%) | | 1 | | |
| Minimal | 12 | 5(41.67%) | | 2.37 | 0.558–10.08 | |
| Gross | 19 | 11(57.89%) | | 5.31 | 1.806–15.61 | |
| **N stage** | | | **3.82** | | | **0.15** |
| N0 | 13 | 3(23.07%) | | 1 | | |
| N1a | 25 | 10(40.00%) | | 3.26 | 0.993–10.73 | |
| N1b | 19 | 6(31.58%) | | 1.83 | 0.464–7.222 | |
| **Local persistence or recurrence** | | | **1.55** | | | **0.21** |
| No | 37 | 11(29.73%) | | 1 | | |
| Yes | 20 | 8(40.00%) | | 1.90 | 0.691–5.219 | |
| **Timing of distant metastasis** | | | **0.33** | | | **0.56** |
| At initial presentation | 12 | 4(33.33%) | | 1 | | |
| Delayed distant metastases | 45 | 15(33.33%) | | 0.74 | 0.262–2.076 | |
| **Symptom of distant metastases** | | | **5.23** | | | **0.02** |
| Asymptomatic | 30 | 8(26.67%) | | 1 | | |
| Symptomatic | 27 | 11(40.74%) | | 3.12 | 2.177–8.256 | |
| **Site of distant metastases at initial diagnosis** | | | **5.08** | | | **0.02** |
| Pulmonary only | 33 | 7(21.21%) | | 1 | | |
| Extrapulmonary | 24 | 12(50.00%) | | 2.92 | 1.150–7.435 | |
| **Treatment modalities of distant metastases** | | | **0.05** | | | **0.83** |
| RAI treatment | 40 | 12(30.00%) | | 1 | | |
| RAI combined with other treatment | 17 | 7(41.18%) | | 1.11 | 0.431–2.870 | |
| **$^{131}$I avidity** | | | **0.09** | | | **0.76** |
| Yes | 32 | 11(34.38%) | | 1 | | |
| No | 25 | 8(32.00%) | | 1.16 | 0.454–2.936 | |
| **RR-DTC** | | | **6.24** | | | **0.01** |
| No | 22 | 2(9.09%) | | 1 | | |
| Yes | 35 | 17(48.57%) | | 3.29 | 1.293–8.383 | |

cancer-specific survival in PTC patients with distant metastases (36). These unexpected results may be explained by statistical deviations from the relative frequency of gross extrathyroidal extension in FTC (37). In this study, we found that gross extrathyroidal extension was an independent prognostic factor for elderly DTC patients with distant metastasis upon initial diagnosis that was associated with poor OS and DSS. An explanation for this finding may be that elderly patients with gross extrathyroidal extension tend to show more dedifferentiation, which can increase the formation of metastatic lesions (38).

In previous reports, the incidence of non-$^{131}$I-avid distant metastases in DTC patients was approximately 30% (14, 25, 30, 31, 39, 40). In this study, distant metastatic lesions did not accumulate $^{131}$I in 43.86% (25/57) of the patients, which is higher than previous reports. This could suggest that distant metastatic lesions are less likely to have $^{131}$I uptake in elderly (>65-years-old) patients than in those <45-years-old (41). However, this finding could also represent differences caused by selection bias, small sample sizes, and/or screening methods for the referral population in our department and/or in clinical management measures after DTC diagnosis. Any of these factors could also affect the incidence of non- $^{131}$I uptake in elderly DTC patients with distant metastases. $^{131}$I avidity is the strongest prognostic factor for survival in DTC patients with distant metastases. Some studies have indicated that

**TABLE 5 |** Multivariate analysis of prognostic factors for the disease-specific survival (DSS) of the elderly differentiated thyroid cancer (DTC) patients presenting with distant metastasis according to Cox's Proportional Hazards Model at the end of follow-up.

| Variable | No. of patients | Hazard ratio | 95 % CI | P value |
|---|---|---|---|---|
| **Extrathyroidal extension** | | | | |
| No | 26 | 1 | | |
| Minimal | 12 | 2.01 | 0.528–10.381 | 0.13 |
| Gross | 19 | 4.94 | 1.511–17.319 | 0.02 |
| **Symptom of distant metastases** | | | | |
| Asymptomatic | 30 | 1 | | **0.05** |
| Symptomatic | 27 | 2.02 | 0.992–7.256 | |
| **Site of distant metastases at initial diagnosis** | | | | |
| Pulmonary only | 33 | 1 | | 0.03 |
| Extrapulmonary | 24 | 2.48 | 1.030–9.001 | |
| **RR-DTC** | | | | |
| No | 22 | 1 | | 0.02 |
| Yes | 35 | 2.89 | 1.378–9.017 | |

$^{131}$I avidity was associated with longer OS, DSS, progression-free survival, and disease-free survival compared cases without $^{131}$I avidity (14, 25, 30, 31, 39, 40). However, we found no difference in the median OS or DSS between $^{131}$I avid and non-$^{131}$I avid cases. A possible explanation for this finding is that in some elderly DTC patients, although the metastatic lesions could absorb $^{131}$I, they had insufficient $^{131}$I uptake or resistance to the effects of $^{131}$I therapy, so disease progression was found during $^{131}$I treatment and/or follow-up. The classification of RR-DTC has been widely used in clinical practice recently. A literature report showed that approximately 50% of DTC patients with distant metastases were evaluated as RR-DTC (42), which has an important impact on survival data, as the mean survival time of these patients is approximately 3–5 years and their 10-year OS rate is usually <10% (11). In our study, 35 (61.40%) elderly patients with distant metastases were estimated to be RR-DTC using the univariate and multivariate analyses, which was higher than previous reports and suggested that elderly WDTC patients with distant metasets had higher levels of dedifferentiation and poorer prognosis. Our study also revealed that RR-DTC was an independent factor for poor OS and DSS.

In addition to $^{131}$I treatment, other treatment modalities are usually used for RR-DTC with distant metastases, such as external radiotherapy, palliative surgery, chemotherapy, bisphosphonates, and interventional therapy. Currently, there is no curative treatment modality available except for complete surgical resection, which is not always possible. Generally, RR-DTC is not sensitive to external radiotherapy or chemotherapy. Although TKIs such as sorafenib and lenvatinib have been recommend for RR-DTC by the ATA management guidelines (11), the challenge of using these drugs is how to maintain their continued use and control their adverse effects; moreover, many clinical trials have shown that TKI treatment can only improve the PFS and objective response rate, but has limited efficacy in prolonging OS (21, 22). In this study, $^{131}$I combined with other treatment modalities were performed in 29.8% (17/57) of the elderly patients with distant metastases. When we compared outcomes with patients who only received $^{131}$I treatment, there was no evidence that $^{131}$I combined with other treatments

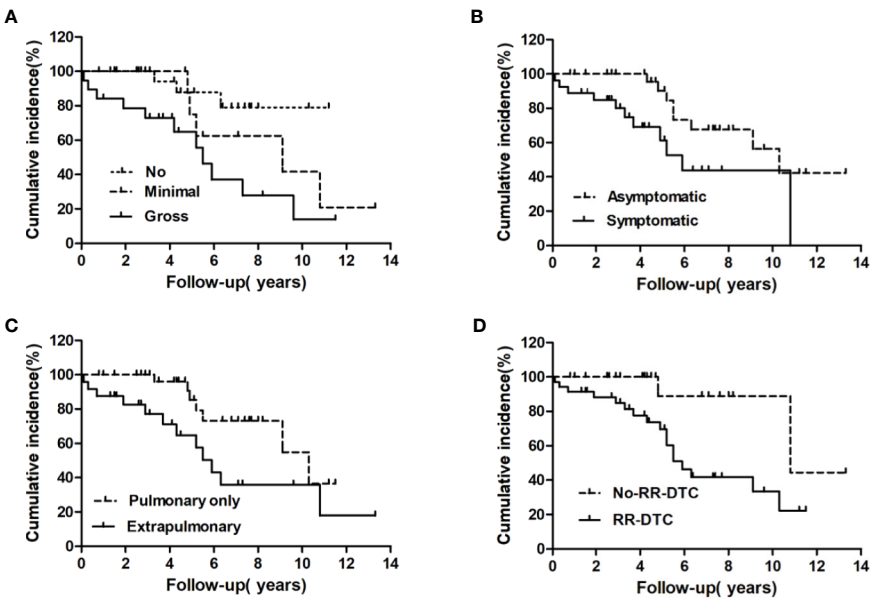


**FIGURE 5** | Univariate analysis of the prognostic factors for median DSS at the end of follow-up; the median disease-specific survival (DSS) of patients differed significantly according to extrathyroidal extension **(A)**, the presence of symptomatic metastases **(B)**, site of distant metastases at initial diagnosis **(C)**, and RR-DTC status **(D)**.

improved the median OS or DSS of these elderly patients with distant metastases.

The primary limitations of this study were as follows: first, it has certain inherent limitations related to its retrospective observational nature; nonetheless, this is the first study to evaluate the clinical outcomes of elderly patients with distant metastases from WDTC. Second, as the study spanned a long period, selection bias may have occurred. Third, because this was a single-center study conducted in China, further studies are needed to confirm the repeatability of our results in other countries and with other races. Moreover, except for standardized $^{131}$I treatment, the individualized treatment model and incomplete acquisition of treatment data may have led to deviations in clinical outcomes.

In summary, to the best of our knowledge, this is the first study to evaluate the long-term outcomes and prognostic factors of distant metastases in elderly WDTC patients and included the largest series of patients treated with $^{131}$I at a single center to date. We found that the 5- and 10-year OS rates for these elderly patients with distant metastases from WDTC were 71.50% and 30.49%, respectively, while their 5- and 10-year DSS rates were 76.89% and 48.71%, respectively. Absence of or minimal extrathyroidal extension and non-RR-DTC were independent factors associated with improved OS, while absence of or minimal extrathyroidal extension, lung-only metastases, and non-RR-DTC were independent prognostic factors related to improved DSS in these patients. These findings may contribute to clinical decision-making during the treatment and follow-up of elderly DTC patients with distant metastases. However, the sample size should be further increased, and a future perspective study is needed to obtain more thorough conclusions.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The study protocol was approved by the Ethics Committee of the Shanghai Jiao Tong University Affiliated Sixth People's Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

Z-LQ and Q-YL designed the study. Z-KS, C-TS, Z-LQ, and G-QZ conducted the statistical analysis. YW, H-JS, and CX collected the clinical data. Z-LQ wrote the whole paper. Z-LQ, Q-YL, and YW supervised and edited the paper. All authors contributed to the article and approved the submitted version.

## FUNDING

This work was supported by the National Natural Science Foundation of China (grant number 81771865 and 81901773), the Shanghai Key Discipline of Medical Imaging (grant number 2017ZZ02005), and retrospective research fund of the Shanghai Sixth People's Hospital.

## ACKNOWLEDGMENTS

We thank James P. Mahaffey, PhD, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

## REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* (2018) 68(1):7–30. doi: 10.3322/caac.21442
2. Matrone A, Campopiano MC, Nervo A, Sapuppo G, Tavarelli M, De Leo S. Differentiated Thyroid Cancer, From Active Surveillance to Advanced Therapy: Toward a Personalized Medicine. *Front Endocrinol (Lausanne)* (2020) 10:884. doi: 10.3389/fendo.2019.00884
3. Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin Endocrinol Metab* (2001) 86(4):1447–63. doi: 10.1210/jcem.86.4.7407
4. Chereau N, Trésallet C, Noullet S, Godiris-Petit G, Tissier F, Leenhardt L, et al. Prognosis of papillary thyroid carcinoma in elderly patients after thyroid resection: A retrospective cohort analysis. *Med (Baltimore)* (2016) 95(47): e5450–e. doi: 10.1097/MD.0000000000005450
5. Shteinshnaider M, Muallem Kalmovich L, Koren S, Or K, Cantrell D, Benbassat C. Reassessment of Differentiated Thyroid Cancer Patients Using the Eighth TNM/AJCC Classification System: A Comparative Study. *Thyroid* (2018) 28(2):201–9. doi: 10.1089/thy.2017.0265
6. Har-El G, Sidi J, Kahan E, Segal K, Abraham A. Thyroid cancer in patients 70 years of age or older. Retrospective study of 50 patients. *Ann Otol Rhinol Laryngol* (1987) 96(4):403–10. doi: 10.1177/000348948709600411
7. Kauffmann RM, Hamner JB, Ituarte PHG, Yim JH. Age greater than 60 years portends a worse prognosis in patients with papillary thyroid cancer: should there be three age categories for staging? *BMC Cancer* (2018) 18(1):316–. doi: 10.1186/s12894-018-0319-6
8. Lang BH-H, Wong KP, Cheung CY, Wan KY, Lo C-Y. Evaluating the prognostic factors associated with cancer-specific survival of differentiated thyroid carcinoma presenting with distant metastasis. *Ann Surg Oncol* (2013) 20(4):1329–35. doi: 10.1245/s10434-012-2711-x
9. Hirsch D, Levy S, Tsvetov G, Gorshtein A, Slutzky-Shraga I, Akirov A, et al. LONG-TERM OUTCOMES AND PROGNOSTIC FACTORS IN PATIENTS WITH DIFFERENTIATED THYROID CANCER AND DISTANT METASTASES. *Endocr Pract* (2017) 23(10):1193–200. doi: 10.4158/EP171924.OR
10. Song H-J, Qiu Z-L, Shen C-T, Wei W-J, Luo Q-Y. Pulmonary metastases in differentiated thyroid cancer: efficacy of radioiodine therapy and prognostic factors. *Eur J Endocrinol* (2015) 173(3):399–408. doi: 10.1530/EJE-15-0296
11. 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* (2016) 26(1):1–133. doi: 10.1089/thy.2015.0020

12. Ferrari SM, Ruffilli I, Centanni M, Virili C, Materazzi G, Alexopoulou M, et al. Lenvatinib in the Therapy of Aggressive Thyroid Cancer: State of the Art and New Perspectives with Patents Recently Applied. *Recent Pat Anticancer Drug Discov* (2018) 13(2):201–8. doi: 10.2174/1574892813666180220110729
13. Corrado A, Ferrari SM, Politti U, Mazzi V, Miccoli M, Materazzi G, et al. Aggressive thyroid cancer: targeted therapy with sorafenib. *Minerva Endocrinol* (2017) 42(1):64–76. doi: 10.23736/S0391-1977.16.02229-X
14. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab* (2006) 91(8):2892–9. doi: 10.1210/jc.2005-2838
15. Qiu Z-L, Shen C-T, Luo Q-Y. Clinical management and outcomes in patients with hyperfunctioning distant metastases from differentiated thyroid cancer after total thyroidectomy and radioactive iodine therapy. *Thyroid* (2015) 25 (2):229–37. doi: 10.1089/thy.2014.0233
16. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* (2017) 67(2):93–9. doi: 10.3322/caac.21388
17. Qiu Z-L, Song H-J, Xu Y-H, Luo Q-Y. Efficacy and survival analysis of 131I therapy for bone metastases from differentiated thyroid cancer. *J Clin Endocrinol Metab* (2011) 96(10):3078–86. doi: 10.1210/jc.2011-0093
18. Qiu Z-L, Wei W-J, Sun Z-K, Shen C-T, Song H-J, Zhang X-Y, et al. Circulating Tumor Cells Correlate with Clinicopathological Features and Outcomes in Differentiated Thyroid Cancer. *Cell Physiol Biochem* (2018) 48(2):718–30. doi: 10.1159/000491898
19. Nishino M, Jagannathan JP, Ramaiya NH, Van den Abbeele AD. Revised RECIST guideline version 1.1: What oncologists want to know and what radiologists need to know. *AJR Am J Roentgenol* (2010) 195(2):281–9. doi: 10.2214/AJR.09.4110
20. Costelloe CM, Chuang HH, Madewell JE, Ueno NT. Cancer Response Criteria and Bone Metastases: RECIST 1.1, MDA and PERCIST. *J Cancer* (2010) 1:80–92. doi: 10.7150/jca.1.80
21. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* (2014) 384 (9940):319–28. doi: 10.1016/S0140-6736(14)60421-9
22. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med* (2015) 372(7):621–30. doi: 10.1056/NEJMoa1406470
23. Han JM, Bae JC, Kim HI, Kwon S, Jeon MJ, Kim WG, et al. Clinical Outcomes of Differentiated Thyroid Cancer Patients with Local Recurrence or Distant Metastasis Detected in Old Age. *Endocrinol Metab (Seoul)* (2018) 33(4):459–65. doi: 10.3803/EnM.2018.33.4.459
24. Ruegemer JJ, Hay ID, Bergstralh EJ, Ryan JJ, Offord KP, Gorman CA. Distant metastases in differentiated thyroid carcinoma: a multivariate analysis of prognostic variables. *J Clin Endocrinol Metab* (1988) 67(3):501–8. doi: 10.1210/jcem-67-3-501
25. Slook O, Levy S, Slutzky-Shraga I, Tsvetov G, Robenshtok E, Shimon I, et al. LONG-TERM OUTCOMES AND PROGNOSTIC FACTORS IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA AND BONE METASTASES. *Endocr Pract* (2019) 25(5):427–37. doi: 10.4158/EP-2018-0465
26. Schlumberger M, Tubiana M, De Vathaire F, Hill C, Gardet P, Travagli JP, et al. Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. *J Clin Endocrinol Metab* (1986) 63(4):960–7. doi: 10.1210/jcem-63-4-960
27. Shoup M, Stojadinovic A, Nissan A, Ghossein RA, Freedman S, Brennan MF, et al. Prognostic indicators of outcomes in patients with distant metastases from differentiated thyroid carcinoma. *J Am Coll Surg* (2003) 197(2):191–7. doi: 10.1016/S1072-7515(03)00332-6
28. Benbassat CA, Mechlis-Frish S, Hirsch D. Clinicopathological characteristics and long-term outcome in patients with distant metastases from differentiated thyroid cancer. *World J Surg* (2006) 30(6):1088–95. doi: 10.1007/s00268-005-0472-4
29. Sampson E, Brierley JD, Le LW, Rotstein L, Tsang RW. Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. *Cancer* (2007) 110(7):1451–6. doi: 10.1002/cncr.22956
30. Mihailovic J, Stefanovic L, Malesevic M, Markoski B. The importance of age over radioiodine avidity as a prognostic factor in differentiated thyroid carcinoma with distant metastases. *Thyroid* (2009) 19(3):227–32. doi: 10.1089/thy.2008.0186
31. Lee J, Soh E-Y. Differentiated thyroid carcinoma presenting with distant metastasis at initial diagnosis clinical outcomes and prognostic factors. *Ann Surg* (2010) 251(1):114–9. doi: 10.1097/SLA.0b013e3181b7faf6
32. Huang IC, Chou F-F, Liu R-T, Tung S-C, Chen J-F, Kuo M-C, et al. Long-term outcomes of distant metastasis from differentiated thyroid carcinoma. *Clin Endocrinol (Oxf)* (2012) 76(3):439–47. doi: 10.1111/j.1365-2265.2011.04231.x
33. Lin J-D, Kuo S-F, Huang B-Y, Lin S-F, Chen S-T. The efficacy of radioactive iodine for the treatment of well-differentiated thyroid cancer with distant metastasis. *Nucl Med Commun* (2018) 39(12):1091–6. doi: 10.1097/MNM.0000000000000897
34. Albano D, Panarotto MB, Durmo R, Rodella C, Bertagna F, Giubbini R. Clinical and prognostic role of detection timing of distant metastases in patients with differentiated thyroid cancer. *Endocrine* (2019) 63(1):79–86. doi: 10.1007/s12020-018-1713-2
35. Vuong HG, Duong UNP, Pham TQ, Tran HM, Oishi N, Mochizuki K, et al. Clinicopathological Risk Factors for Distant Metastasis in Differentiated Thyroid Carcinoma: A Meta-analysis. *World J Surg* (2018) 42(4):1005–17. doi: 10.1007/s00268-017-4206-1
36. Lee YK, Kim D, Shin DY, Lee CR, Lee EJ, Kang S-W, et al. The Prognosis of Papillary Thyroid Cancer with Initial Distant Metastasis is Strongly Associated with Extensive Extrathyroidal Extension: A Retrospective Cohort Study. *Ann Surg Oncol* (2019) 26(7):2200–9. doi: 10.1245/s10434-019-07314-x
37. Lang BH-H, Lo C-Y, Chan W-F, Lam K-Y, Wan K-Y. Prognostic factors in papillary and follicular thyroid carcinoma: their implications for cancer staging. *Ann Surg Oncol* (2007) 14(2):730–8. doi: 10.1245/s10434-006-9207-5
38. Gosain R, Alexander JS, Gill A, Perez C. Radioactive Iodine-Refractory Differentiated Thyroid Cancer in the Elderly. *Curr Oncol Rep* (2018) 20 (10):82–. doi: 10.1007/s11912-018-0736-4
39. Schlumberger M, Challeton C, De Vathaire F, Travagli JP, Gardet P, Lumbroso JD, et al. Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma. *J Nucl Med* (1996) 37 (4):598–605.
40. Shaha AR, Shah JP, Loree TR. Differentiated thyroid cancer presenting initially with distant metastasis. *Am J Surg* (1997) 174(5):474–6. doi: 10.1016/s0002-9610(97)00158-x
41. Verburg FA, Mäder U, Tanase K, Thies E-D, Diessl S, Buck AK, et al. Life expectancy is reduced in differentiated thyroid cancer patients ≥ 45 years old with extensive local tumor invasion, lateral lymph node, or distant metastases at diagnosis and normal in all other DTC patients. *J Clin Endocrinol Metab* (2013) 98(1):172–80. doi: 10.1210/jc.2012-2458
42. Wassermann J, Bernier M-O, Spano J-P, Lepoutre-Lussey C, Buffet C, Simon J-M, et al. Outcomes and Prognostic Factors in Radioiodine Refractory Differentiated Thyroid Carcinomas. *Oncologist* (2016) 21(1):50–8. doi: 10.1634/theoncologist.2015-0107


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 15 March 2021
doi: 10.3389/fendo.2021.556851

# Sonographic Characteristics of Papillary Thyroid Carcinoma With Coexistent Hashimoto's Thyroiditis in the Preoperative Prediction of Central Lymph Node Metastasis

*Sijie Chen*[1,2], *Chengcheng Niu*[1,2]*, *Qinghai Peng*[1,2] *and Kui Tang*[1,2]

[1] Department of Ultrasound Diagnosis, The Second Xiangya Hospital, Central South University, Changsha, China, [2] Research Center of Ultrasonography, The Second Xiangya Hospital, Central South University, Changsha, China

OPEN ACCESS

**Edited by:**
Christoph Reiners,
University Hospital Würzburg,
Germany

**Reviewed by:**
Trevor Edmund Angell,
University of Southern California,
United States
Xing Hua,
Army Medical University, China
Zhou Yang,
Southwest Jiaotong University, China

***Correspondence:**
Chengcheng Niu
niuchengcheng@csu.edu.cn

**Specialty section:**
This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology

**Received:** 29 April 2020
**Accepted:** 23 February 2021
**Published:** 15 March 2021

**Citation:**
Chen S, Niu C, Peng Q and Tang K (2021) Sonographic Characteristics of Papillary Thyroid Carcinoma With Coexistent Hashimoto's Thyroiditis in the Preoperative Prediction of Central Lymph Node Metastasis. Front. Endocrinol. 12:556851. doi: 10.3389/fendo.2021.556851

The purpose of this study was to evaluate the usefulness of the sonographic characteristics of papillary thyroid carcinoma (PTC) with Hashimoto's thyroiditis (HT) for predicting central lymph node metastasis (CLNM). One hundred thirty-three patients who underwent thyroidectomy and central cervical lymph node dissection for PTC with coexistent HT were retrospectively analyzed. All PTCs with HT were preoperatively evaluated by ultrasound (US) regarding their nodular number, size, component, shape, margin, echogenicity, calcification, capsule contact with protrusion, vascularity and contrast enhanced ultrasound (CEUS) parameters. Univariate analysis demonstrated that patients with PTCs with HT and CLNM more frequently had age ≤ 45 years, size > 10 mm, a wider than tall shape, microcalcification, hypo-enhancement and peak intensity index < 1 than those without CLNM (all $p<0.05$). Binary logistic regression analysis demonstrated that size > 10 mm and CEUS hypo-enhancement were independent characteristics for the presence of CLNM. Our study indicated that preoperative US characteristics could offer help in predicting CLNM in PTCs with coexistent HT.

**Keywords: contrast enhanced ultrasound, papillary thyroid carcinoma, conventional ultrasound, Hashimoto's thyroiditis, central lymph node metastasis (CLNM)**

## INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignant tumor with a significantly increased incidence in recent years (1–3). Although PTC has an indolent course with a low mortality rate and satisfactory long-term prognosis, cervical lymph node metastasis remains an important factor associated with local recurrence and distant metastasis (4–7). Zaydfudim et al. identified 30,504 PTC patients (49% > 45 years old) and 2,584 follicular carcinoma patients (55% > 45 years old). The study by these researchers found that cervical lymph node metastases conferred an increased risk of death in all patients with follicular carcinoma and in those patients with PTC who were > 45 years old (8). A retrospective analysis of 399 patients demonstrated that prophylactic central compartment (level VI) neck

dissection (CCND) improved disease-free survival in patients with intermediate- and high-risk differentiated thyroid carcinoma (9).

According to the American Thyroid Association's (ATA's) guidelines, PTC patients with clinically involved central lymph nodes (CLNs) are strongly recommended to undergo therapeutic CCND, while PTC patients with clinically uninvolved CLNs can be considered for prophylactic CCND (10). However, prophylactic CCND can result in overtreatment and lead to nerve injury to the voice, permanent hypoparathyroidism and airway function compromise (7).

Preoperative neck US for the cervical lymph nodes is recommended to evaluate the range of surgery, especially for lymph node dissection according to the ATA's guidelines (10). However, approximately 90% of CLNMs might not be found preoperatively (11), since the sensitivity of conventional US for CLNM is less than 50% (4, 12–14). Thus, it is urgently important to identify the risk factors for PTCs with CLNM to design individualized surgical treatment strategies to avoid unnecessary prophylactic lymph node dissection.

Hashimoto's thyroiditis (HT) is one of the most common autoimmune thyroid diseases. HT can cause the destruction of the thyrocytes by lymphocytic infiltration and interstitial fibrosis, and it results in thyroid nodules with atypical sonographic features for overlapping morphologies, margins, echogenicities and internal bloodstreams between benign and malignant lesions against an HT background. It also induces lymphadenopathy in the central compartment, which can increase the difficulty of judging metastatic lymph nodes by sonography (15).

Some authors have evaluated the biological behavior of PTC with CLNM associated with US features (16–19). In addition the widespread application of conventional B-mode US as the basis of examination, the additional use of contrast-enhanced ultrasound (CEUS) could elucidate the micro-vasculature and improve the diagnostic accuracy of thyroid nodules (20–23). However, to the best of our knowledge, the capability of CEUS for predicting CLNM in PTCs with coexistent HT has been only rarely reported. In this study, we studied the clinical characteristics and conventional US and CEUS features of PTCs with coexistent HT with or without CLNM and explored the ability to predict CLNM in PTCs against an HT background.

# MATERIALS AND METHODS

## Patients

The study was approved by the ethics committee of the Second Xiangya Hospital of Central South University in China and was performed in accordance with the Declaration of Helsinki for human studies. From May 2016 to December 2018, 177 consecutive patients who had been preoperatively examined using conventional US and CEUS and had undergone surgery were enrolled in this retrospective study. The inclusion criteria were as follows: (i) pathological examination confirming PTCs with HT after surgery; (ii) patients who underwent conventional US and CEUS examinations.

Forty-two patients were excluded because they did not undergo central lymph node dissection. Two patients were excluded because they had different types of thyroid cancers: 1 medullary thyroid carcinoma and 1 follicular cancer. In patients with multifocal PTCs, only the largest was selected. In addition, thyroid-stimulating hormone (TSH), free thyroxine, free triiodothyronine, thyroid peroxidase antibody (A-TPO) and thyroglobulin antibody (A-TG) were measured in all of the patients before pathological examination. Thus, 133 patients (19 men and 114 women, age mean: 40.92 ± 11.21 y, range: 18-74 y) with 133 PTCs were ultimately included (**Figure 1**).

## Conventional US and Color Doppler US

All of the images in our study were acquired with Siemens Acuson S3000 US scanner (Siemens Medical Solutions, Mountain View, CA, USA) equipped with a 9L4 linear array transducer (4-9 MHz) for conventional US and CEUS. All of the selected thyroid nodules were evaluated for the following US features: size (largest diameter); composition (solid or mixed); shape (taller than wide or wider than tall); margins (well-defined or ill-defined); echogenicity (marked hypo-echoic, hypo-echoic, iso-echoic or hyper-echoic); calcification (no calcification, microcalcification<1 mm in diameter, macrocalcification >1 mm in diameter; the presence of both microcalcification and macrocalcification was defined as microcalcification); capsule contact with protrusion (present or absent); halo sign (present or absent); and internal vascularity (present or absent).

## CEUS and Analysis

Contrast pulsed sequencing (CPS) technology and dedicated analysis software (Contrast Dynamics, Mountain View, CA, USA) were used for CEUS. Three-milliliter SonoVue microbubbles (Bracco, Italy) were injected intravenously, followed by a saline flush of 5 mL. The thyroid nodule imaging lasted 60 s; the time intensity curves (TICs) within selected regions of interest (ROIs) were acquired. CEUS features of the thyroid nodules were classified as follows: enhancement type, compared with surrounding thyroid parenchyma enhancement (hyper-enhancement, iso-enhancement or hypo-enhancement); enhancement uniformity (heterogeneous enhancement or homogeneous enhancement); perfusion pattern (centripetal perfusion, the perfusion of microbubbles from the periphery to the center; centrifugal perfusion, the perfusion of microbubbles from the center to the periphery); surrounding ring enhancement, with the surrounding of the nodule revealing a ring enhancement (hyper ring enhancement, hypo ring enhancement or no ring enhancement); peak intensity (PI, expressed as a percentage); time to peak (TP, expressed in seconds); area under the curve (AUC, expressed as a percentage by seconds); and washout time (WT, expressed in seconds). PI index, TP index, AUC index and WT index are reported as indices by the ratio of the ROIs of nodules to the ROIs of thyroid parenchymal tissue.

## Statistical Analysis

SPSS software (SPSS, Chicago, IL, USA), version 21.0, was used for statistical analyses. The mean ± standard deviation (SD) was used to express continuous data, and the independent t-test was used to compare them. Percentages were used to express categorical data, and the $\chi^2$test were used to analyze them. Binary logistic regression was used to assess independent

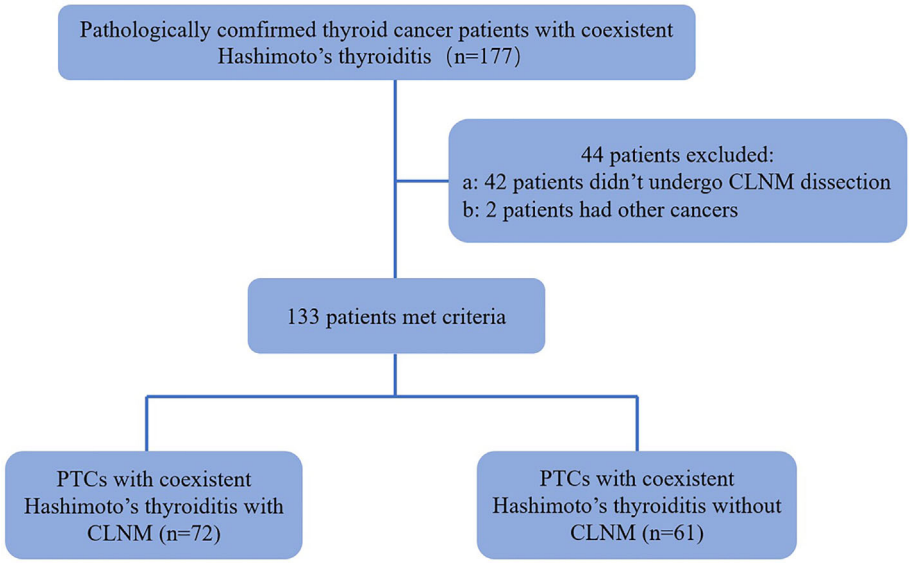


**FIGURE 1** | Flowchart for the selection of thyroid cancer patients. PTC, papillary thyroid carcinoma; CLNM, Central Lymph Node Metastasis.

factors in PTCs with coexistent HT and CLNM. $p<0.05$ indicated significant differences.

## RESULTS

A total of 133 patients with PTCs with coexistent HT, 72 (54.1%) with CLNM and 61 (45.9%) without CLNM, were included in the analysis. The clinical characteristics of the patients are shown in **Table 1**. One hundred fourteen (85.7%) PTC patients with HT were female, and 19 (14.3%) were male. Male patients constituted 16.7% of patients with CLNM and 11.5% of patients without CLNM ($p$ = 0.394). The average age of PTC patients with HT with or without CLNM was 38.29 ± 10.78 years (range: 18-66 years) or 44.03 ± 10.99 years (range: 23-74 years), respectively. Fifty-three (73.6%) patients with CLNM were younger than 45 years, while only 29 (47.5%) patients without CLNM were younger than 45 years ($p$ = 0.002), showing that the

**TABLE 1** | Clinical characteristics of PTC patients with Hashimoto's thyroiditis based on CLNM.

| Characteristics | CLNM | | *P* Value |
|---|---|---|---|
| | Yes (n=72) | No (n=61) | |
| Sex | | | 0.394 |
| Male | 12 (16.7) | 7 (11.5) | |
| Female | 60 (83.3) | 54 (88.5) | |
| Age (years) | 38.29 ± 10.78 | 44.03 ± 10.99 | 0.003* |
| ≤ 45 y | 53 (73.6) | 29 (47.5) | 0.002* |
| > 45 y | 19 (26.4) | 32 (52.5) | |
| Multifocality | | | 0.839 |
| Yes | 26 (36.1) | 21 (34.4) | |
| No | 46 (63.9) | 40 (65.6) | |
| TSH | | | 0.968 |
| Normal | 59 (81.9) | 51 (83.6) | |
| Increased | 9 (12.5) | 7 (11.5) | |
| Decreased | 4 (5.6) | 3 (4.9) | |
| A-TG | | | 0.610 |
| Normal | 23 (31.9) | 17 (27.9) | |
| Increased | 49 (68.1) | 44 (72.1) | |
| A-TPO | | | 0.330 |
| Normal | 17 (23.6) | 19 (31.1) | |
| Increased | 55 (76.4) | 42 (68.9) | |

*CLNM, Central Lymph Node Metastasis; TSH, thyroid-stimulating hormone; A-TG, thyroglobulin antibody; A-TPO, thyroid peroxidase antibody.*
**p < 0.05 was considered a significant difference.*

patients with CLNM were more inclined to be younger. Twenty-six (36.1%) patients with CLNM had multifocal cancers, and 21 (34.4%) patients without CLNM had multifocal cancers ($p$ = 0.839). Forty-nine (68.1%) HT patients with CLNM had increased A-TG levels, and 55 (76.4%) had increased A-TPO levels, whereas 44 (72.1%) HT patients without CLNM had increased A-TG levels, and 42 (68.9%) had increased A-TPO levels ($p$ = 0.610 and $p$ = 0.330).

The US features of the patients are reported in **Table 2**. In patients with multifocal PTCs, only the largest was selected. The mean diameters of PTCs with or without CLNM were 16.03 ± 7.62 mm (range: 6-40 mm) and 10.77 ± 5.14 mm (range: 4-26 mm),

**TABLE 2** | Ultrasonographic nodule characteristics of PTC patients coexisted with Hashimoto's thyroiditis based on CLNM.

| Characteristics | CLNM | | *P* Value |
|---|---|---|---|
| | Yes (n=72) | No (n=61) | |
| **Conventional US parameters** | | | |
| Size (mm) | 16.03 ± 7.62 | 10.77 ± 5.14 | 0.000* |
| >10 mm | 52 (72.2) | 24 (39.3) | 0.000* |
| ≤10 mm | 20 (27.8) | 37 (60.7) | |
| Shape | | | 0.019* |
| Taller than wide | 13 (18.1) | 22 (36.1) | |
| Wider than tall | 59 (81.9) | 39 (63.9) | |
| Margin | | | 0.653 |
| Well-defined | 12 (16.7) | 12 (19.7) | |
| Ill-defined | 60 (83.3) | 49 (80.3) | |
| Echogenicity | | | 0.060 |
| Marked hypoechoic | 15 (20.8) | 9 (14.8) | |
| Hypoechoic | 52 (72.2) | 52 (85.2) | |
| Iso- or hyperechoic | 5 (7.0) | 0 (0.0) | |
| Calcification | | | 0.046* |
| Absent or macrocalcification | 10 (13.9) | 17 (27.9) | |
| Microcalcification | 62 (86.1) | 44 (72.1) | |
| Capsule contact with protrusion | | | 0.070 |
| Yes | 20 (27.8) | 9 (14.8) | |
| No | 52 (72.3) | 52 (85.2) | |
| Halo sign | | | 0.199 |
| Yes | 17 (23.6) | 9 (14.8) | |
| No | 55 (76.4) | 52 (85.2) | |
| Internal vascularity | | | 0.610 |
| Yes | 23 (31.9) | 17 (27.9) | |
| No | 49 (68.1) | 44 (72.1) | |
| **CEUS parameters** | | | |
| Enhancement type | | | 0.012* |
| Hyper- or iso-enhancement | 16 (22.2) | 26 (42.6) | |
| Hypo-enhancement | 56 (77.8) | 35 (57.4) | |
| Enhancement uniformity | | | 0.869 |
| Heterogeneous enhancement | 51 (70.8) | 44 (72.1) | |
| Homogeneous enhancement | 21 (29.2) | 17 (27.9) | |
| Perfusion pattern | | | 0.538 |
| Centripetal | 65 (90.3) | 53 (86.9) | |
| Centrifugal | 7 (9.7) | 8 (13.1) | |
| Surrounding ring enhancement | | | 0.549 |
| Hyper ring enhancement | 6 (8.3) | 4 (6.6) | |
| Hypo ring enhancement | 2 (2.8) | 4 (6.6) | |
| No ring enhancement | 64 (88.9) | 53 (86.8) | |
| PI index | | | 0.011* |
| ≥ 1 | 14 (19.4) | 24 (39.3) | |
| < 1 | 58 (80.6) | 37 (60.7) | |
| TP index | | | 0.760 |
| ≥ 1 | 64 (90.3) | 56 (91.8) | |
| < 1 | 8 (9.7) | 5 (8.2) | |
| AUC index | | | 0.074 |
| ≥ 1 | 10 (13.9) | 16 (26.2) | |
| < 1 | 62 (86.1) | 45 (73.8) | |
| WT index | | | 0.947 |
| ≥ 1 | 8 (11.1) | 7 (11.5) | |
| < 1 | 64 (88.9) | 54 (88.5) | |

*PI, peak intensity; TP, time to peak; AUC, area under the curve; WT, washout time.*
**p < 0.05 was considered a significant difference.*

respectively, and the mean diameters of the former were significantly larger than those of the latter ($p$ = 0.000). Fifty-two (72.2%) patients with CLNM had size > 10 mm, while only 24 (39.3%) patients without CLNM had size > 10 mm ($p$ = 0.000). For PTCs with coexistent HT with or without CLNM, all of the nodules were solid in this study. In the PTCs with CLNM group, 60 (83.3%) the nodules had ill-defined margins (**Figure 2**), 52 (72.2%) nodules exhibited hypoechoic echogenicity (**Figure 2**), 5 (7.0%) nodules exhibited isoechoic or hyperechoic echogenicity (**Figure 3**), 62 (86.1%) nodules had microcalcification (**Figures 2** and **3**), 20 (27.8%) nodules had capsule contact with protrusion (**Figure 2**), 17 (23.6%) had the hypoechoic halo sign (**Figure 2**), and 23 (31.9%) nodules had internal blood flow (**Figures 2** and **3**). For CEUS parameters, 56 (77.8%) nodules exhibited hypo-enhancement (**Figure 2**), and 16 (22.2%) nodules exhibited hyper or iso-enhancement (**Figure 3**), indicating that the majority of the nodules underwent lower enhancement than those in parenchymal tissue. Fifty-one (70.8%) nodules showed heterogeneous enhancement (**Figure 2**), and 21 (29.2%) nodules showed homogeneous enhancement (**Figure 3**), indicating that most of the nodules received an ununiform perfusion of microbubbles. Sixty-five (90.3%) nodules had the centripetal perfusion pattern (**Figures 2** and **3**), representing most of the nodules receiving the perfusion of microbubbles from the periphery to the center. Six (8.3%) nodules existed hyper-ring enhancement (**Figures 2** and **3**). The quantitative CEUS parameters showed that 14 (19.4%) nodules had a PI index ≥1 (**Figure 3**), indicating that 19.4% of nodules had a higher PI than

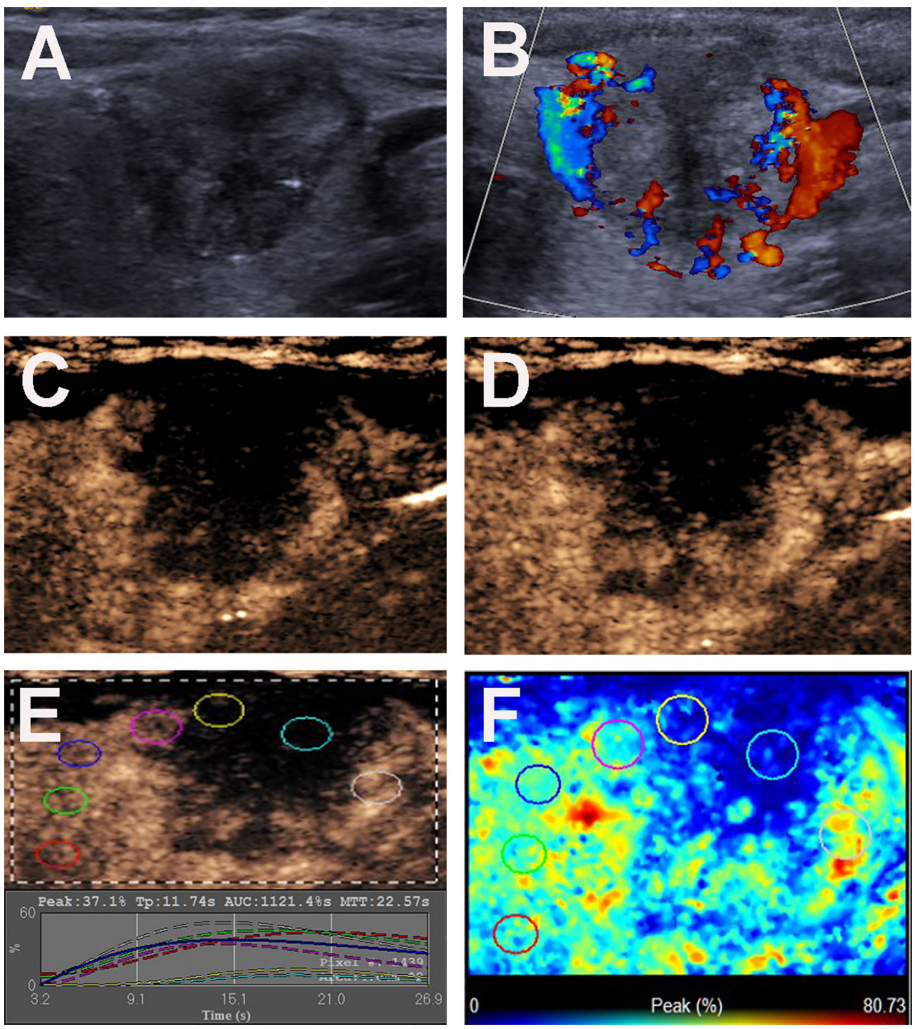


**FIGURE 2** | Conventional US and CEUS images of a 36-y-old female PTC patient with Hashimoto's thyroiditis of the left thyroid lobe with CLNM. **(A)** B-mode US image revealing an 18.6-mm solid thyroid nodule with hypo-echogenicity, ill-defined margins, microcalcification, capsule contact with protrusion and halo sign. **(B)** Doppler image revealing abundant peripheral and slight internal vascularity. **(C, D)** CEUS images revealing a centripetal heterogeneous hypo-enhancement with a surrounding incomplete ring of thyroid nodule from the periphery to the center, at **(C)** 8s (wash-in) and **(D)** 13s (time to peak). **(E)** TICs of the thyroid nodule and peripheral thyroid parenchyma with different ROIs (different color circles). **(F)** Parametric color map indicating the PI values for the center of nodule was lower than those of the periphery of nodule and adjacent thyroid parenchyma.

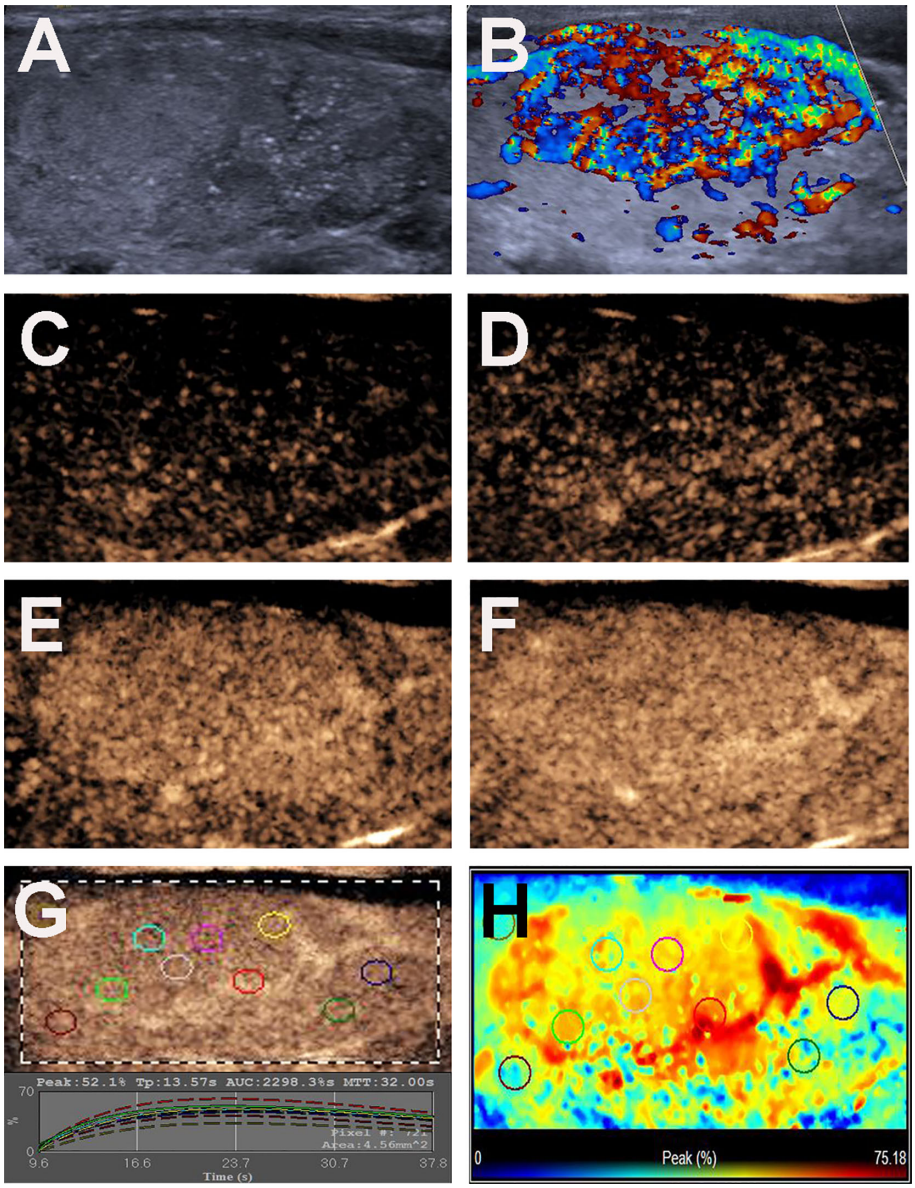


**FIGURE 3** | Conventional US and CEUS images of a 31-y-old female PTC patient with Hashimoto's thyroiditis of the right thyroid lobe with CLNM. **(A)** B-mode US image revealing a 35.0-mm solid thyroid nodule with iso-echogenicity, ill-defined margins and microcalcification. **(B)** Doppler image revealing abundant peripheral and internal vascularity. **(C–F)** CEUS images revealing a centripetal homogeneous hyperenhancement with an incomplete ring of thyroid nodule from the periphery to the center, at **(C)** 11s (wash-in), **(D)** 12s, **(E)** 14s and **(F)** 17s (time to peak). **(G)** TICs of the thyroid nodule and peripheral thyroid parenchyma with different ROIs (different color circles). **(H)** Parametric color map indicating the PI values for the center of nodule was lower than that of the periphery of nodule, but higher than that of adjacent thyroid parenchyma.

those of parenchymal tissue. Ten (13.9%) nodules had an AUC index ≥1 (**Figure 3**), representing that 13.9% of nodules had a larger AUC than those of the parenchymal tissue.

n the PTCs without CLNM group, 22 (36.1%) nodules had taller than wider shapes (**Figure 4**), 49 (80.3%) nodules had ill-defined margins (**Figure 4**), and 52 (85.2%) nodules exhibited hypoechoic echogenicity (**Figure 4**). For CEUS parameters, 26 (42.6%) nodules exhibited hyper- or iso-enhancement (**Figure 4**), 17 (27.9%) nodules showed homogeneous enhancement (**Figure 4**), 53 (86.9%) nodules had the centripetal perfusion pattern (**Figure 4**), and 53 (86.8%) showed no ring enhancement (**Figure 4**). The quantitative CEUS parameters showed that 24 (39.3%) nodules had a PI index ≥1 (**Figure 4**), 56 (91.8%) nodules had a TP index ≥1 (**Figure 4**), and 16 (26.2%) nodules had an AUC index ≥1 (**Figure 4**). Univariate analyses indicated that PTCs with coexistent HT with CLNM more often

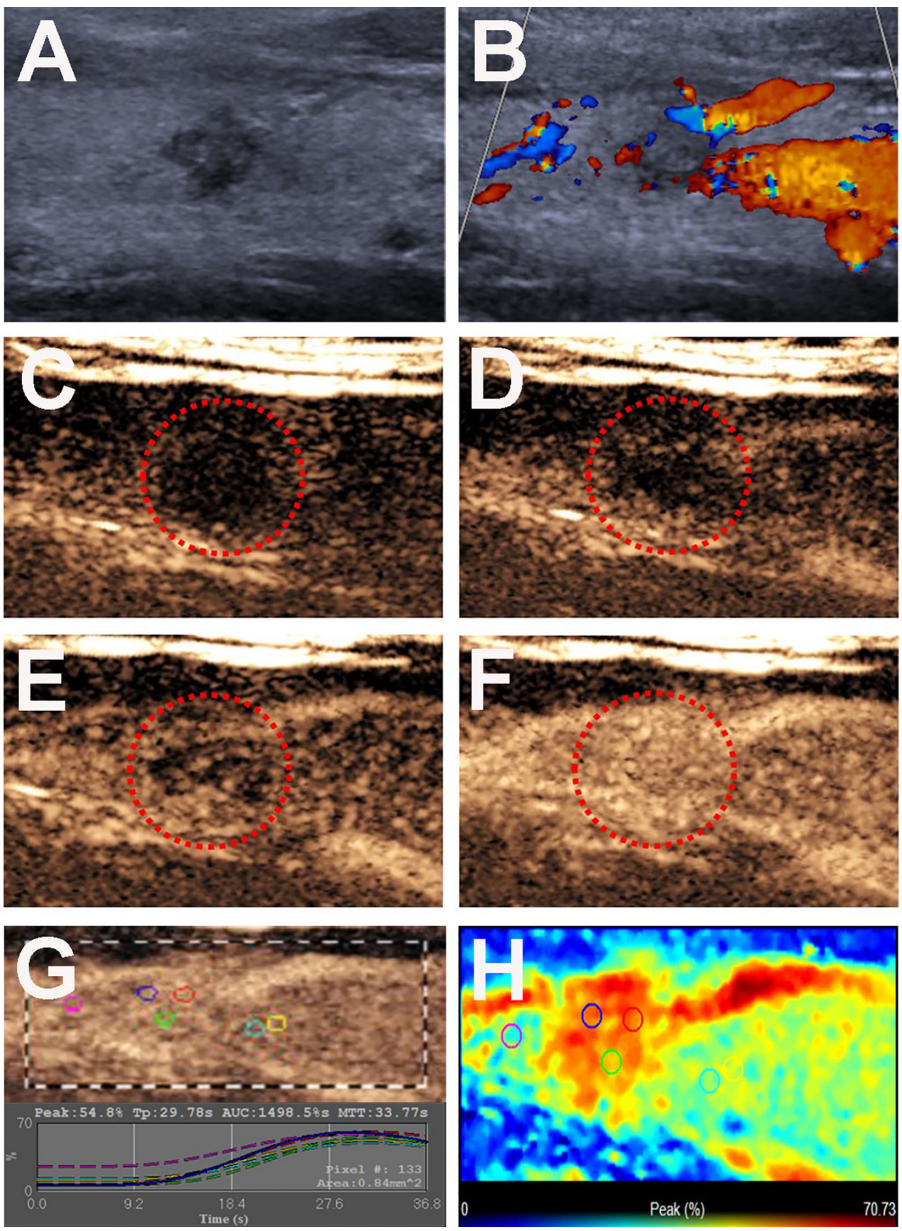


**FIGURE 4** | Conventional US and CEUS images of a 26-y-old male PTC patient with Hashimoto's thyroiditis of the right thyroid lobe without CLNM. **(A)** B-mode US image revealing a 8.0-mm solid thyroid nodule with a taller than wider shape, hypo-echogenicity, ill-defined margins. **(B)** Doppler image revealing abundant peripheral vascularity and no obvious internal vascularity. **(C–F)** CEUS images revealing a centripetal homogeneous hyperenhancement of thyroid nodule from the periphery to the center, at **(C)** 2s, **(D)** 20s (wash-in), **(E)** 22s and **(F)** 34s (time to peak). **(G)** TICs of the thyroid nodule and peripheral thyroid parenchyma with different ROIs (different color circles). **(H)** Parametric color map indicating the PI values for the nodule was higher than that of adjacent thyroid parenchyma.

had size > 10 mm, wider than taller shape, microcalcification, hypo-enhancement and peak intensity indices < 1 compared those without CLNM (all $p < 0.05$).

Binary logistic regression analysis was performed on all of the ultrasonographic statistically significant variables ($p < 0.05$). The results indicated that size > 10 mm (B= 1.460, OR = 4.306, 95% CI = 2.239-8.278, p=0.000) and CEUS hypo-enhancement (B = 1.064, OR =2.899, 95% CI = 1.457-5.767, p=0.002) were independent characteristics for the presence of CLNM (**Table 3**).

## DISCUSSION

High-resolution US is a popular method for the preoperative diagnosis of PTC and the evaluation of cervical lymph nodes. Previous studies have reported that PTC with CLNM is associated with a poor prognosis; however, not all CLNMs can be detected by US preoperatively (6, 11).

In the present study, univariate analysis showed that age ≤ 45 years was a clinical risk factor associated with CLNM in PTC

**TABLE 3** | Multivariate logistic regression analysis of association of CLNMs and US characteristics in PTC patients with Hashimoto's thyroiditis.

| Parameter | B | SE | Odds ratio | 95% CI | *P* |
|---|---|---|---|---|---|
| Size > 10 mm | 1.460 | 0.334 | 4.306 | 2.239-8.278 | 0.000* |
| Hypo-enhancement | 1.064 | 0.351 | 2.899 | 1.457-5.767 | 0.002* |

**p < 0.05 was considered a significant difference.*

patients with coexistent HT, showing that patients with CLNM were more inclined to be young people. Similar findings have been reported by other authors (17, 24, 25).

Recently, a few studies showed that US features were helpful for predicting CLNM in PTC patients. Kim et al. found that size >1 cm and markedly hypoechoic echogenicity were identified to be prognostic factors predicting CLNM (18). Nam et al. retrospectively reviewed 488 patients who underwent surgery for PTC. Malignant-looking PTCs (M-PTCs) more frequently had LN metastasis, extrathyroidal extension, and a higher stage than benign-looking PTCs (B-PTCs), especially when tumor size > 1 cm (19). In our study, we found that the tumor size > 10 mm was one of the predictive factors for CLNM.

For malignant nodules, among the US features, microcalcification, internal flow, capsule contact and involvement were identified to be independent prognostic factors for predicting CLNM (17). Subsequently, researchers found that tumor size < 10 mm was also an independent factor for CLNM in PTCs (4). In this study, on univariate analysis, we found that a wider than taller shape and microcalcification were significantly associated with CLNM of PTCs with HT, and the former perhaps contributed to the size of thyroid nodules. In this study of 22 PTCs with taller than wider shape in the non-CLNM group, 21 nodules had a size ≤ 10 mm, and the other nodule had a size > 10 mm and < 20 mm, indicating that smaller-sized thyroid nodules were more inclined to exhibit the taller than wider shape of PTCs in HT patients. Regarding microcalcification, as one of the predictive factors for CLNM, as also reported by other studies (17, 25), was exhibited in 62 (86.1%) PTCs with CLNM and 44 (72.1%) PTCs without CLNM in this study.

CEUS detects more tumor microvessels than the color Doppler techniques. Some studies have reported that CEUS could improve the diagnostic accuracy of thyroid nodes (22, 23). However, few studies have reported the association of CEUS characteristics with the predicting of CLNM in PTC patients, especially with coexistent HT. In a study by Huang et al., hyper- or iso-enhancement was predictive of the presence of CLNM (25). Hyper- or iso-enhancement suggests that the tumor blood supply is greater or equal to the surrounding thyroid parenchyma. Hypo-enhancement indicates that the tumor blood supply is less than in the surrounding thyroid parenchyma. However, in our study, 42 (31.6%) PTCs with HT showed hyper- or iso-enhancing parametric maps, while only 16 (38.1%) of these patients presented with CLNM, which was significantly less than in HT patients with PTCs without CLNM (61.9%). The results indicated that hypo-enhancement in PTC patients with HT was considerably more frequent in the CLNM group than in the non-CLNM group, inconsistent with the study of Hong et al. (25). Similarly, the peak intensity index was significant lower in HT patients with PTCs with CLNM than that of HT patients with PTCs without CLNM. Due to the destruction of thyrocytes by lymphocytic infiltration and interstitial fibrosis in HT disease, the thyroid parenchyma displayed changes in echogenicity and blood supply; the abundant blood supply in the thyroid parenchyma could strengthen the parenchymal enhancement in CEUS mode and bring out a lower nodule enhancement by contrast, which was variable for the degrees of lymphocytic infiltration and interstitial fibrosis. To the best of our knowledge, these CEUS parameters for predicting CLNM in PTCs with coexistent HT have not been explored to date. According to the results of binary logistic regression analysis, tumor size >10 mm and CEUS hypo-enhancement were independent characteristics for the presence of CLNM in PTC patients with coexistent HT. If a young PTC patient has a thyroid tumor size > 10 mm and CEUS hypo-enhancement preoperatively, prophylactic CCND is suggested according to this study.

This study had several limitations. First, only patients with pathological results were enrolled, some of the PTC patients did not undergo surgery, and some of the PTCs subjected to thyroidectomy without central lymph node dissection were missed; thus, selection bias was present. Second, the nodule size differences in this study were enormous, which might have affected the US characteristics of PTCs. A large-scale and prospective multicenter study is needed to clarify these findings.

## CONCLUSIONS

In HT patients, age ≤ 45 years, size > 10 mm, wider than tall shape, microcalcification, hypo-enhancement and peak intensity index <1 in the preoperative US and CEUS findings were significantly associated with CLNM of PTCs. Multivariate analysis demonstrated that tumor size > 10 mm and CEUS hypo-enhancement were independent characteristics for the presence of CLNM. Thus, preoperative US characteristics could be helpful in predicting CLNM in PTC patients with HT.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the Second Xiangya Hospital of Central South University in China. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

CN contributed to the conception and design of the work. SC and CN participated to data analysis and manuscript writing. QP and KT participated to data collection and patients' follow-up. All authors contributed to the article and approved the submitted version.

## FUNDING

This project was funded by the National Natural Science Foundation of China (Grant No. 81974267), Hunan Provincial Natural Science Foundation of China (Grant 2018JJ2575) and Hunan Provincial Health Commission Research Foundation Project (B2019166).

## REFERENCES

1. Davies L, Welch HG. Current thyroid cancer trends in the United States. *JAMA Otolaryngol Head Neck Surg* (2014) 140(4):317–22. doi: 10.1001/jamaoto.2014.1
2. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. *JAMA* (2017) 317 (13):1338–48. doi: 10.1001/jama.2017.2719
3. Cho BY, Choi HS, Park YJ, Lim JA, Ahn HY, Lee EK, et al. Changes in the clinicopathological characteristics and outcomes of thyroid cancer in Korea over the past four decades. *Thyroid* (2013) 23(7):797–804. doi: 10.1089/thy.2012.0329
4. Chen J, Li XL, Zhao CK, Wang D, Wang Q, Li MX, et al. Conventional Ultrasound, Immunohistochemical Factors and BRAF(V600E) Mutation in Predicting Central Cervical Lymph Node Metastasis of Papillary Thyroid Carcinoma. *Ultrasound Med Biol* (2018) 44(11):2296–306. doi: 10.1016/j.ultrasmedbio.2018.06.020
5. Ito Y, Kihara M, Takamura Y, Kobayashi K, Miya A, Hirokawa M, et al. Prognosis and prognostic factors of papillary thyroid carcinoma in patients under 20 years. *Endocr J* (2012) 59(7):539–45. doi: 10.1507/endocrj.ej12-0086
6. Baek SK, Jung KY, Kang SM, Kwon SY, Woo JS, Cho SH, et al. Clinical risk factors associated with cervical lymph node recurrence in papillary thyroid carcinoma. *Thyroid* (2010) 20(2):147–52. doi: 10.1089/thy.2008.0243
7. Carling T, Long WD. 3rd and R. Udelsman: Controversy surrounding the role for routine central lymph node dissection for differentiated thyroid cancer. *Curr Opin Oncol* (2010) 22(1):30–4. doi: 10.1097/CCO.0b013e328333ac97
8. Zaydfudim V, Feurer ID, Griffin MR, Phay JE. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. *Surgery* (2008) 144(6):1070–7; discussion 1077-8. doi: 10.1016/j.surg.2008.08.034
9. Medas F, Canu GL, Cappellacci F, Anedda G, Conzo G, Erdas E, et al. Prophylactic Central Lymph Node Dissection Improves Disease-Free Survival in Patients with Intermediate and High Risk Differentiated Thyroid Carcinoma: A Retrospective Analysis on 399 Patients. *Cancers (Basel)* (2020) 12(6):1658. doi: 10.3390/cancers12061658
10. 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* (2016) 26(1):1–133. doi: 10.1089/thy.2015.0020
11. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* (2009) 19 (11):1167–214. doi: 10.1089/thy.2009.0110
12. 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* (2015) 25(12):1351–4. doi: 10.1089/thy.2015.0176
13. Lee DW, Ji YB, Sung ES, Park JS, Lee YJ, Park DW, et al. Roles of ultrasonography and computed tomography in the surgical management of cervical lymph node metastases in papillary thyroid carcinoma. *Eur J Surg Oncol* (2013) 39(2):191–6. doi: 10.1016/j.ejso.2012.07.119
14. Hwang HS, Orloff LA. Efficacy of preoperative neck ultrasound in the detection of cervical lymph node metastasis from thyroid cancer. *Laryngoscope* (2011) 121(3):487–91. doi: 10.1002/lary.21227
15. Jankovic B, Le KT, Hershman JM. Clinical Review: Hashimoto's thyroiditis and papillary thyroid carcinoma: is there a correlation? *J Clin Endocrinol Metab* (2013) 98(2):474–82. doi: 10.1210/jc.2012-2978
16. Liu W, Cheng R, Ma Y, Wang D, Su Y, Diao C, et al. Establishment and validation of the scoring system for preoperative prediction of central lymph node metastasis in papillary thyroid carcinoma. *Sci Rep* (2018) 8(1):6962. doi: 10.1038/s41598-018-24668-6
17. 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. *Eur Radiol* (2016) 26(8):2611–22. doi: 10.1007/s00330-015-4088-2
18. Kim SS, Lee BJ, Lee JC, Kim SJ, Lee SH, Jeon YK, et al. Preoperative ultrasonographic tumor characteristics as a predictive factor of tumor stage in papillary thyroid carcinoma. *Head Neck* (2011) 33(12):1719–26. doi: 10.1002/hed.21658
19. Nam SY, Shin JH, Han BK, Ko EY, Ko ES, Hahn SY, et al. Preoperative ultrasonographic features of papillary thyroid carcinoma predict biological behavior. *J Clin Endocrinol Metab* (2013) 98(4):1476–82. doi: 10.1210/jc.2012-4072
20. Peng Q, Niu C, Zhang M, Chen S. Sonographic Characteristics of Papillary Thyroid Carcinoma with Coexistent Hashimoto's Thyroiditis: Conventional Ultrasound, Acoustic Radiation Force Impulse Imaging and Contrast-Enhanced Ultrasound. *Ultrasound Med Biol* (2019) 45(2):471–80. doi: 10.1016/j.ultrasmedbio.2018.10.020
21. Deng J, Zhou P, Tian SM, Zhang L, Li JL, Qian Y. Comparison of diagnostic efficacy of contrast-enhanced ultrasound, acoustic radiation force impulse imaging, and their combined use in differentiating focal solid thyroid nodules. *PLoS One* (2014) 9(3):e90674. doi: 10.1371/journal.pone.0090674
22. Zhang Y, Zhou P, Tian SM, Zhao YF, Li JL, Li L. Usefulness of combined use of contrast-enhanced ultrasound and TI-RADS classification for the differentiation of benign from malignant lesions of thyroid nodules. *Eur Radiol* (2017) 27(4):1527–36. doi: 10.1007/s00330-016-4508-y
23. Ma JJ, Ding H, Xu BH, Xu C, Song LJ, Huang BJ, et al. Diagnostic Performances of Various Gray-Scale, Color Doppler, and Contrast-Enhanced Ultrasonography Findings in Predicting Malignant Thyroid Nodules. *Thyroid* (2014) 24(2):355–63. doi: 10.1089/thy.2013.0150
24. Zhao Q, Ming J, Liu C, Shi L, Xu X, Nie X, et al. Multifocality and total tumor diameter predict central neck lymph node metastases in papillary thyroid microcarcinoma. *Ann Surg Oncol* (2013) 20(3):746–52. doi: 10.1245/s10434-012-2654-2
25. Hong YR, Yan CX, Mo GQ, Luo ZY, Zhang Y, Wang Y, et al. Elastography, and contrast enhanced US features of papillary thyroid microcarcinoma predict central compartment lymph node metastases. *Sci Rep 5* (2015) 5:7748. doi: 10.1038/srep07748

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 25 March 2021
doi: 10.3389/fendo.2021.591015

# Diagnostic Model Incorporating Clinicopathological Characteristics of Delphian Lymph Node Metastasis Risk Profiles in Papillary Thyroid Cancer

*Xingchen Li[1†], Yuansheng Duan[1†], Dandan Liu[1†], Hongwei Liu[2†], Mengqian Zhou[1], Kai Yue[1], Yanjie Shuai[1], Yu Wang[1], Chenyan Ji[1], Chao Jing[1*], Yansheng Wu[1*] and Xudong Wang[1*]*

[1] Department of Maxillofacial & E.N.T. Oncology, Tianjin Medical University Cancer Institute & Hospital, Key Laboratory of Cancer Prevention and Therapy, Tianjin Cancer Institute, National Clinical Research Center of Cancer, Tianjin, China, [2] Department of Epidemiology and Biostatistics, School of Public Health, Tianjin Medical University, Tianjin, China

The Delphian lymph node (DLN), also known as the prelaryngeal node, is one component of the central lymph node. The DLN has been well studied in laryngeal cancer, although its significance in papillary thyroid cancer (PTC) remains unclear. We retrospectively analyzed 936 patients with PTC who underwent thyroidectomy by a single surgeon in Tianjin Cancer Hospital from 2017 to 2019. Moreover, 250 PTC patients who underwent thyroidectomy by another surgeon in Tianjin Cancer Hospital from January 2019 to April 2019 were used as a validation cohort. Among the 936 patients with PTC, 581 patients (62.1%) had DLNs, of which 177 samples with metastasis (177/581, 30.5%) were verified. DLN metastasis was significantly correlated with sex, age, tumor size, bilateral cancer, multifocality, extrathyroidal extension, lymphovascular invasion and central and lateral neck lymph node metastasis. Multivariate analysis revealed that independent risk factors for DLN metastasis included age, gender, tumor size, extrathyroid extension, lymphovascular invasion and central lymph node metastasis, which determined the nomogram. In particular, tumor size was proven to be one of the most predominant single predictors. The diagnostic model had an area under the curve (AUC) of 0.829 (95% confidence interval, 0.804–0.854). The internal and external validations of the nomogram were 0.819 and 0.745, respectively. Our results demonstrate that DLN metastasis appears to be a critical parameter for predicting metastatic disease of the central compartments. Furthermore, this study provides a precise criterion for assessing DLN metastasis and has great clinical significance for treating PTC.

**Keywords: risk factor, nomogram, diagnostic model, papillary thyroid cancer, Delphian lymph node**

OPEN ACCESS

***Edited by:***
*Christoph Reiners, University Hospital Würzburg, Germany*

***Reviewed by:***
*Giorgio Napolitano, University of Studies G. d'Annunzio Chieti and Pescara, Italy*
*Nicolas Schlegel, Julius Maximilian University of Würzburg, Germany*

***Correspondence:**
*Xudong Wang*
*WXD.1133@163.com*
*Yansheng Wu*
*yansheng1981@163.com*
*Chao Jing*
*SuperDwell@hotmail.com*

*†These authors have contributed equally to this work*

***Specialty section:***
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

***Received:*** *03 August 2020*
***Accepted:*** *01 February 2021*
***Published:*** *25 March 2021*

***Citation:***
*Li X, Duan Y, Liu D, Liu H, Zhou M, Yue K, Shuai Y, Wang Y, Ji C, Jing C, Wu Y and Wang X (2021) Diagnostic Model Incorporating Clinicopathological Characteristics of Delphian Lymph Node Metastasis Risk Profiles in Papillary Thyroid Cancer. Front. Endocrinol. 12:591015. doi: 10.3389/fendo.2021.591015*

## INTRODUCTION

Thyroid neoplasms are the fifth most prevalent malignancy in women and account for 3% of all human malignancies (1). Papillary thyroid carcinoma (PTC) is the most common histopathological subtype, accounting for approximately 90% of all thyroid carcinomas (2). Although the 20-year overall survival rate of PTC reaches up to 90% and its disease-specific survival rate is approximately 97% (3), metastasis to regional cervical lymph nodes occurs early and frequently, and the rate of lymph node metastasis is as high as 90% in PTC (4). The central neck nodes are the most common sites of nodal metastasis in PTC patients (5, 6). Emerging evidence has suggested that cervical lymph node metastasis acts as an unfavorable factor that contributes to locoregional recurrence (7–9).

The DLN, also known as the prelaryngeal or precricoid lymph node, usually consists of a single node or a group of lymph nodes and receives lymphatic drainage from the larynx and thyroid (10, 11). The Delphian, pretreacheal, and paratracheal lymph node groups compose the central neck lymph nodes. Increasing evidence indicates that DLN metastasis is an effective predictor of regional lymph node disease and recurrence in many malignant head and neck cancers, including PTC (12–16). Currently, the role of DLN metastasis in PTC has gained substantial attention (17–19). Reports have indicated that DLN metastasis is an aggressive disease and predicts a high risk of recurrence in PTC (14, 20). At the moment, it is controversial whether clinically lymph node-negative (cN0) PTC patients should undergo prophylactic central lymph node dissection. The DLN, one component of central neck node clusters, may be an available preoperative indicator to help surgeons to make individualized treatment plans. Hence, a high-efficiency DLN metastasis evaluation system will be of clinical significance.

Thus far, DLN has been well studied in laryngeal cancer while its role in thyroid cancer remains unknown. The aim of this study was to assess the incidence and risk factors of DLN metastasis, and to develop a clinicopathologic characters-based diagnostic model to help surgeons predict preoperative DLN metastasis.

## MATERIALS AND METHODS

### Patients

We reviewed 936 patients who were diagnosed pathologically with PTC. All the patients underwent thyroidectomy by a single surgeon at the Head and Neck Surgery Department of Tianjin Cancer Hospital from June 2017 to January 2019. The precricoid region was deliberately excised and labeled as DLNs (**Figure 1**) and then diagnosed by histopathology. Overall, 250 patients who underwent thyroidectomy by another surgeon at Tianjin Cancer Hospital from January 2019 to April 2019 were used as a validation cohort to evaluate the performance of the diagnostic model. Of the 250 patients with PTC, 127 (50.8%) patients were found to have DLNs. DLN metastasis was observed in 28 (22.4%) patients. The mean number of metastatic DLNs was 1.89. The clinicopathologic information was gathered, and the protocol in this study was approved by the Tianjin Cancer Hospital Ethics Committee.

### Surgery

All the patients underwent thyroidectomy according to the Chinese practice guidelines in thyroid cancer (21, 22). For bilateral PTC patients, Total thyroidectomy was performed. For unilateral PTC patients, total thyroidectomy or lobectomy plus isthmusectomy were performed. When unilateral PTC patients met one of following conditions: tumor size >4 cm, multifocal in one lobe, extrathyroid invasion or distant metastasis, which were diagnosed by the use of frozen section analysis and preoperative examination, total thyroidectomy plus isthmusectomy may be considered, according to the guidelines of Chinese Thyroid Association. Meanwhile, pretracheal nodes, ipsolateral or bilateral paratracheal nodes, and peripheral fatty tissue were routinely dissected. The DLNs were removed once they were identified by the surgeon. Ipsilateral prophylactic central node dissection (pCND) was performed in cN0 PTC patients. When any of the cervical lymph nodes were verified as suspicious through preoperative ultrasonography, palpation or intraoperative inspection, a contralateral CND was performed. If lateral neck lymph node (Level II-V) was suspected with

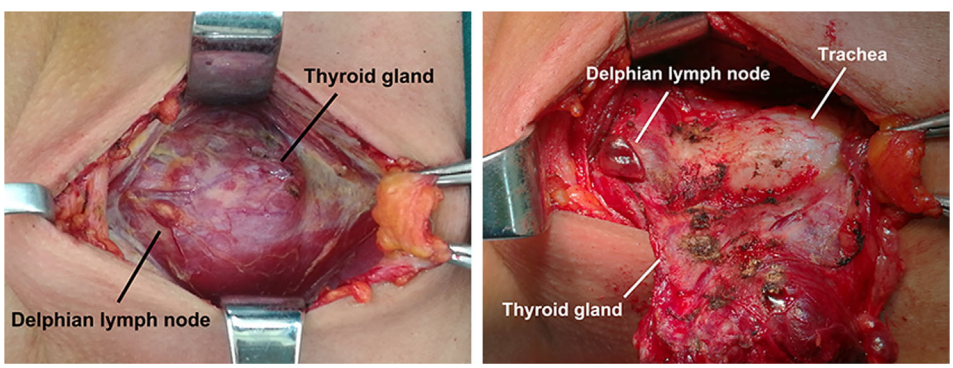


**FIGURE 1** | The Delphian lymph node (DLN).

metastasis by preoperative ultrasound examination or affirmed with metastasis by fine needle aspiration, lateral node dissection (LND) would be performed.

## Statistical Analysis

The characteristics of patients were displayed as the mean ± SD or frequencies with percentages. The correlation between DLN metastasis and various clinical factors was analyzed by univariable analysis using Student's *t*-test (for continuous variables) or the chi-squared test (for categorical variables). Logistic regression was used to identify the factors that were independently associated with DLN metastasis. The tolerance for all the potential predictors was > 0.1 and the variance inflation factor (VIF) was < 10. A multiple-variable logistic regression model, including all the variables with *P* values less than 0.05 in multivariate analysis, was used for translation into a nomogram diagnostic model. The model performance was assessed using discrimination and calibration (23). A nomogram was created to calculate individual probabilities (24). We evaluated the performance of the diagnosis model in the validation cohort and determined the means and 95% confidence intervals of the AUROC. The analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R-software version 3.5.1 (R foundation for statistical computing, Vienna, Austria. URL http://www.R-project.org).

# RESULTS

## Patient and Clinicopathologic Characteristics

Of all the 936 patients, DLNs were detected in 581 (62.07%, 581/936) patients, and the median numbers of DLNs were 2.1 (range, 1–10). In the group with identified DLNs, 177 (30.46%, 177/581) patients were confirmed to be DLN positive. The percentage of central lymph node metastasis in PTC patients was 59.40% (**Table 1**).

The univariate analysis revealed that metastatic disease to the DLN was associated with male sex (52.5% vs. 22.2%, $p<0.001$), younger age at diagnosis (38.27 ± 11.997 vs. 43.86 ± 10.752, $p<0.001$), larger tumor (13.79 ± 8.8659 vs. 9.38 ± 4.3466, $p<0.001$), bilateral (39.0% vs. 24.9%, $p<0.001$), multifocality (46.3% vs. 30.7%, $p<0.001$), extrathyroid extension (ETE) (87.0% vs. 73.3%, $p<0.001$), lymphovascular invasion (10.7% vs. 1.5%, $p<0.001$), central neck node metastases (43.2% vs. 7.9%, $p<0.001$) and lateral neck node metastases (58.9% vs. 25.0%, $p=0.022$) (**Table 2**), whereas the correlations between DLN metastasis and thyroiditis ($p=0.636$) or tumor location ($p=0.774$) were not statistically significant.

**TABLE 1** | Rates of Delphian lymph node (DLN) detection and metastasis.

| Variables | N/total (%)* |
|---|---|
| DLN detection | 581/936 (62.07%) |
| DLN metastasis | 177/581 (30.46%) |
| Central neck node metastasis | 556/936 (59.40%) |
| Mean no. of DLNs (range) | 2.1 (1–10) |
| Mean no. of DLN metastases (range) | 1.6 (1–9) |

**Unless otherwise indicated.*

**TABLE 2** | Comparison of clinicopathological characteristics between the patients with and without DLN metastasis.

| Variable | No. of DLN-positive patients (%) | No. of DLN-negative patients (%) | *P* value |
|---|---|---|---|
| Gender | | | <0.001 |
| Male | 83 (46.89) | 75 (18.56) | |
| Female | 94 (53.11) | 329 (81.44) | |
| Age (mean ± SD) | 38.27 ± 11.997 | 43.86 ± 10.752 | <0.001* |
| Thyroiditis | | | 0.636 |
| Yes | 44 (24.85) | 108 (26.73) | |
| No | 133 (75.15) | 296 (73.27) | |
| Tumor size (mean ± SD) | 13.79 ± 8.8659 | 9.38 ± 4.3466 | <0.001 |
| Bilateral | | | |
| No | 88 (49.71) | 265 (65.59) | <0.001 |
| Yes | 89 (50.29) | 139 (34.41) | |
| Multifocality | 82 (46.32) | 124 (30.69) | <0.001 |
| Extrathyroid extension | 154 (87.01) | 296 (73.27) | <0.001 |
| Lymphovascular invasion | 19 (10.73) | 6 (1.49) | <0.001 |
| Location of tumor | | | |
| Solitary tumor | 82 (46.33) | 229 (56.68) | 0.208# |
| Upper | 16 | 47 | |
| Middle-upper | 11 | 42 | |
| Middle | 18 | 28 | |
| Middle-lower | 22 | 56 | |
| Lower | 15 | 56 | |
| Multifocal tumor | 95 (53.67) | 175 (43.32) | 0.109& |
| In one lobes | 35 | 48 | |
| In both lobes | 60 | 127 | |
| Central neck node metastases | | | <0.001 |
| Present | 161 (90.96) | 212 (53.12) | |
| Absent | 16 (9.04) | 187 (46.88) | |
| Lateral neck node metastases | | | 0.022 |
| Present | 103 (97.17) | 72 (88.89) | |
| Absent | 3 (2.83) | 9 (11.11) | |

*Data are no. of patients (%) unless otherwise indicated.*
**t test for tumor location analysis; #for solitary tumors, upper vs. upper-middle vs. middle vs. middle-lower vs. lower; &for multifocal tumor, both lobes vs. single lobe.*

All the variables with *P* values less than 0.05 in univariate analysis were selected for multivariate logistic analysis. As shown in **Figure 2**, gender (male, $p<0.0001$), age (younger age, $p=0.0039$), tumor size (>10mm, $p<0.0001$), ETE ($p=0.0081$), lymphovascular invasion ($p=0.0071$) and central neck node metastasis ($p<0.0001$) were independent risk factors of DLN metastasis. However, lateral neck lymph node metastasis was not included in the multivariate logistic analysis due to the limited number of cases. For central compartment metastasis, DLN status had a sensitivity, specificity, positive and negative predictive values of 43%, 92%, 91% and 47%, respectively. And for lateral lymph node metastasis, DLN metastasis had a respective sensitivity, specificity, positive and negative predictive values of 59%, 75%, 97% and 11% (**Table 3**).

## Diagnostic Model Development and Its Validation

A multivariate logistic regression model was adopted to establish the diagnostic model for DLN metastasis. Gender, age, tumor size,

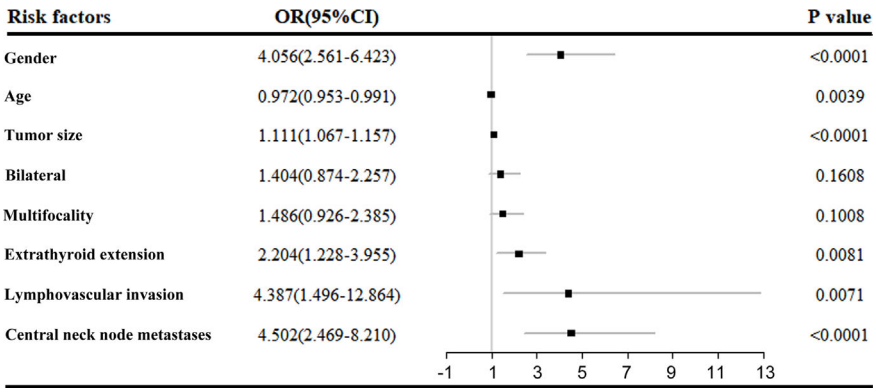


**FIGURE 2** | Multivariate logistic regression analysis of DLN metastasis.

**TABLE 3** | Ability of Delphian node metastasis to predict central and lateral lymph node metastasis.

| Lymph node metastasis types | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | LR+ | LR– |
|---|---|---|---|---|---|---|
| Central | 43 | 92 | 91 | 47 | 5.38 | 0.62 |
| Lateral | 59 | 75 | 97 | 11 | 2.36 | 0.55 |

*PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood radio; LR–, negative likelihood radio.*

ETE, lymphovascular invasion and central neck node metastasis were included as the clinicopathologic features. For internal validation, the study population (n=556) was randomly assigned to training data sets (66%) or test data sets (33%). The diagnostic model was established with the training data while the test data were used to assess model performance with AUC. The area under the ROC curve (AUC) of the training data and testing data was 0.829 (95% CI, 0.804–0.854) and 0.819 (95% CI, 0.764–0.870), respectively (**Figures 3** and **4**). For external validation, 250 PTC patients who underwent thyroidectomy by another surgeon were used to evaluate the performance of the diagnostic model. The area under the ROC curve was 0.745. Calibration plots recalibrated the diagnostic models to predict risk of DLN metastasis. Calibration of the diagnosis model was satisfactory (**Figure 5**).

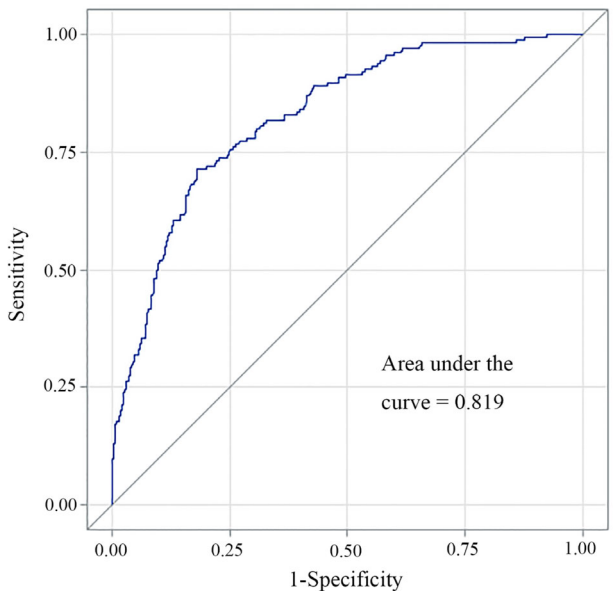


**FIGURE 3** | The AUC of the ROC curve of the proposed methods for the diagnosis of DLN metastasis.

## Risk Factors-Based Nomogram Development

A nomogram was developed to calculate the degree of individual risk in order to improve clinical diagnosis. The nomogram based on these significant variables was established (**Figure 6**). Among the six significant features, tumor size was one predominant predictor of DLN metastasis in the nomogram. When all these criteria were satisfied, the specificity was infinite close to 100%. For example, a 45-year-old man was diagnosed initially with PTC. His tumor size was 3 mm, and central lymph node metastasis on preoperative ultrasonography was positive. ETE was confirmed by intraoperative frozen biopsy, although there was no lymphovascular invasion. The DLNs were excised, and then, histopathological examination showed that the DLN had no metastasis. The probability of DLN metastasis assessed by nomogram was approximately 30%.

## DISCUSSION

Delphian was first used as an eponym for the prelaryngeal node in thyroid disease by Raymond B. Randall, and it is hypothesized that metastasis to this lymph node predicts a poor prognosis from cancer (13, 20). Previous literature has reported that DLN positivity is a measurable parameter to predict extensive lymph node metastasis, recurrence and poor overall survival in

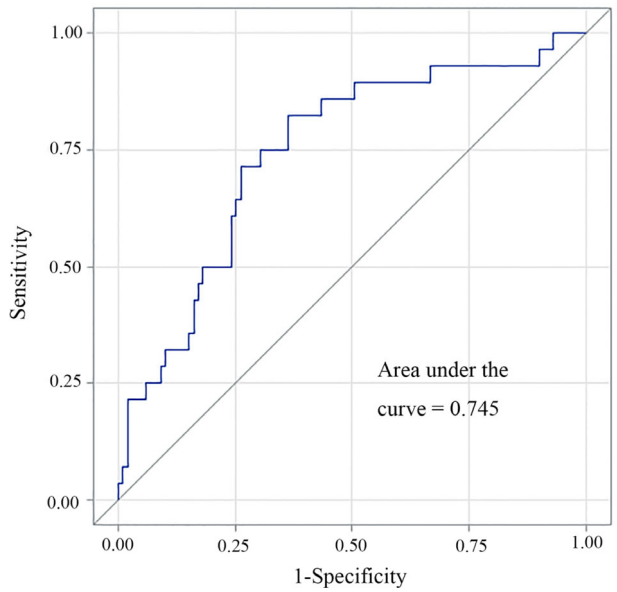


**FIGURE 4** | An external cohort verification of the prediction model for DLN metastasis.

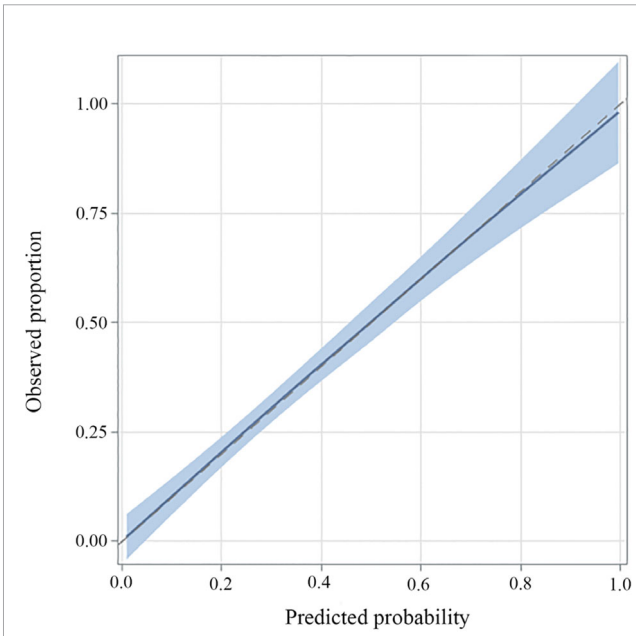


**FIGURE 5** | Calibration plots of recalibrated prognostic models to predict risk of DLN metastasis. In the case of perfect calibration, all the groups of predicted probabilities fit close to the blue diagonal line, corresponding to an intercept of 0 and a slope of 1 for the calibration plot. The vertical lines in grouped observations represent 95% confidence intervals.

laryngeal and hypopharyngeal cancer (25, 26). As for PTC, recent reports detected the DLN in 23% to 75% of PTC patients, and the DLN positivity rate was 8% to 25% (12, 13, 15, 16, 27–30). Metastasis to the DLN is associated with several clinicopathological characteristics of PTC patients, including age, gender, tumor size, tumor location, multifocality, ETE, lymphovascular invasion and central and lateral neck node metastasis (12–14, 16, 27, 28, 30). In our series, male PTC patients were more likely to have positive DLNs. In addition, the rate of positive DLNs in younger patients was higher than that in elderly patients, suggesting that age was negatively correlated with DLN metastasis. Crucially, several adverse prognostic factors in PTC, including ETE, increased volume (number and size) of primary tumor, lymphovascular invasion and central and lateral node metastasis were verified to be positively related to DLN metastasis. Multivariable analyses revealed that gender, age, tumor size, ETE, lymphovascular invasion and central neck node metastasis were independent risk factors.

The DLN receives afferent lymph flow from the larynx and thyroid gland, which then flows towards the central and lateral neck lymph nodes (12). Studies have reported that patients with DLN metastasis are five to eight times more likely to have central compartment disease and 3.5 to 4 times more likely to have lateral neck lymph node metastasis (12–14). DLN positivity is predictive of further central and lateral lymph node metastasis (20). Hence, once metastatic disease to the DLN is identified, the surgeon should pay greater attention to the central and lateral neck compartment. We confirmed that the metastatic rate to the central lymph node and lateral neck lymph node in DLN-positive patients was 161 of 177 (90.96%) and 103/106 (97.17%), respectively. There has been debate over many years regarding whether prophylactic central node dissection should be performed in clinically N0 (cN0) PTC patients, and the prognostic significance of metastasis in this node group is controversial. Although NCCN clinical practice guideline in thyroid carcinoma and the American Thyroid Association guidelines no longer recommend prophylactic central compartment clearance in all cN0 PTC patients (31, 32), the Chinese Thyroid Association guidelines (21, 22) still recommend prophylactic central neck dissection, because the occult neck lymph node metastasis rate in cN0 PTC is still up to 72% (14), which could be the seeds of recurrence. Therefore, the central compartment should still be critically evaluated in all patients with cN0 PTC. The DLN, as one component of Level VI, is relatively sensitive for estimating Level VI metastatic disease. Joseph D. et al. (13) investigated 103 patients with thyroid cancer, and 21.4% of the patients were DLN positive. In that analysis, DLN involvement was associated with greater nodal disease (9.8 vs. 1.6 nodes), larger tumor size (19.4 mm vs. 11.1 mm) and younger age (41 vs. 47 years). Importantly, these anthors confirmed that DLN positivity remarkably predicted further disease in the neck lymph nodes. DLN-positive patients were approximately 8 times, 4 times and 60 times more likely to have central node disease, lateral node disease, and any neck nodal disease respectively. Our results were similar to the data mentioned above. Additionally, in our study, the diameter of the tumor was more than 5mm in 96.05% (170/177) of DLN-positive PTC and more than 10 mm in 66.67%

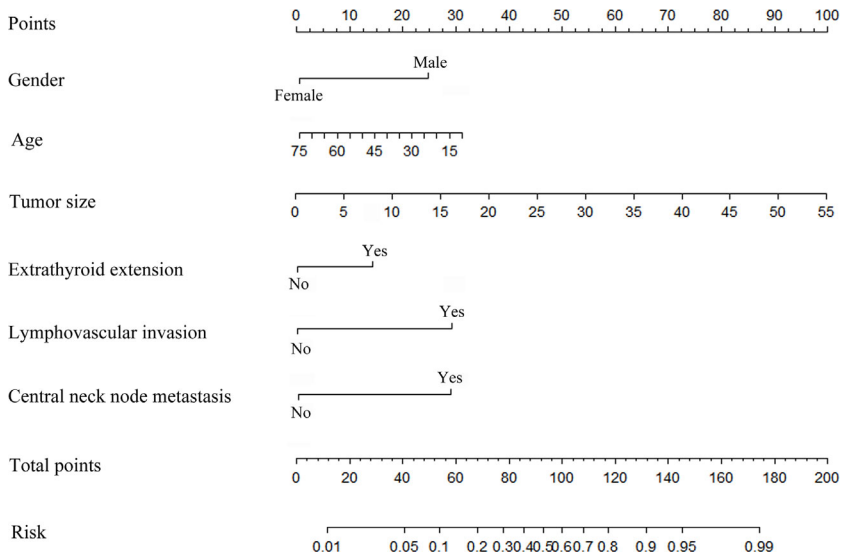


**FIGURE 6** | Risk factor-based nomogram for predicting DLN metastasis. Predictor points ("Points" scale; top) correspond to each variable.

(118/177) of DLN-positive PTC patients. Moreover, our results showed that DLN involvement was predictive of further disease in the central lymph node (sensitivity: 41%, specificity: 92%, positive predictive value (PPV): 91% and negative predictive value (NPV): 60%) and moderately predictive of further disease in the lateral neck compartment (sensitivity: 59%, specificity: 75%, PPV: 97%, NPV: 11%). Collectively, evaluating the status of the DLN is beneficial for the selection of lymph node management. Based on these data, once the status of DLN is sensitively evaluated, we can better predict the criticality of lymph node involvement.

In our study, conclusive evidence of DLN metastasis was obtained by a nomogram that was developed according to all adverse factors. These factors greatly contribute to a high risk of disease metastasis and recurrence (31). Ideally, a more accurate measurement before the operation and evaluation of the frozen sections of samples collected during the operation is essential for diagnosing DLN and Level VI nodal metastases. The nomogram proposed in this study, incorporating independent risk factors, provides a useful tool for surgeons to improve metastatic disease prediction and decision-making. To the best of our knowledge, this is the first retrospective study in PTC patients to search for clinicopathologic risk factors and further develop a diagnostic model for DLN metastasis. However, further studies should be conducted to validate the potential application value of nomograms in PTC patients with suspicious or confirmed DLN metastasis. Admittedly, our study was inherently limited by the retrospective single-center design with a probable selection bias. Moreover, lateral lymph node dissection was performed only when there was evidence of metastasis, which resulted in insufficient enrollment of negative cases. Hence, we excluded lateral lymph node metastasis from the multivariable analyses and the significance of lateral neck node metastasis might be underestimated.

In conclusion, our findings demonstrate that metastatic PTC to the DLN is associated with a number of clinicopathologic characteristics. As the DLN could be a clinical sensitive predictor of further neck lymph nodes, particularly the central compartment, we developed a diagnostic model that includs all adverse factors. If there is strong suspicion of metastatic DLN disease in cN0 PTC, the remainder of the central compartment should be evaluated for further nodal metastasis, and the appropriate dissection should be performed.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

This study was approved by the Medical Ethics Committee of the Tianjin Medical University Cancer Institute & Hospital (bc2020046), and written informed consent was obtained from each patient.

## AUTHOR CONTRIBUTIONS

CJ and YSD conceived and designed the study. XCL, DDL, and HWL collected the clinical information and performed most of the statistical analyses. MQZ, KY, YJS, and YW contributed to the data analysis and interpretation. XDW and YSW provided clinical

samples and information. The manuscript was written by XCL and revised by CJ and YSD. CYJ contributed to the revision of the manuscript. CJ, XDW, and YSW supervised the research. All authors contributed to the article and approved the submitted version.

## ACKNOWLEDGMENTS

This manuscript has been released as a pre-print at https://www.researchsquare.com/article/rs-42289/v1, (33).

## REFERENCES


1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* (2018) 68(1):7–30. doi: 10.3322/caac.21442
2. Mao Y, Xing M. Recent incidences and differential trends of thyroid cancer in the USA. *Endocr Relat Cancer* (2016) 23(4):313–22. doi: 10.1530/ERC-15-0445
3. Ito Y, Miyauchi A, Kihara M, Fukushima M, Higashiyama T, Miya A. Overall Survival of Papillary Thyroid Carcinoma Patients: A Single-Institution Long-Term Follow-Up of 5897 Patients. *World J Surg* (2018) 42(3):615–22. doi: 10.1007/s00268-018-4479-z
4. Wang LY, Ganly I. Nodal metastases in thyroid cancer: prognostic implications and management. *Future Oncol* (2016) 12(7):981–94. doi: 10.2217/fon.16.10
5. So YK, Kim MJ, Kim S, Son YI. Lateral lymph node metastasis in papillary thyroid carcinoma: A systematic review and meta-analysis for prevalence, risk factors, and location. *Int J Surg* (2018) 50:94–103. doi: 10.1016/j.ijsu.2017.12.029
6. Sturgeon C, Yang A, Elaraj D. Surgical Management of Lymph Node Compartments in Papillary Thyroid Cancer. *Surg Oncol Clin N Am* (2016) 25(1):17–40. doi: 10.1016/j.soc.2015.08.013
7. Chow SM, Law SC, Chan JK, Au SK, Yau S, Lau WH. Papillary microcarcinoma of the thyroid-Prognostic significance of lymph node metastasis and multifocality. *Cancer* (2003) 98(1):31–40. doi: 10.1002/cncr.11442
8. Adam MA, Pura J, Goffredo P, Dinan MA, Reed SD, Scheri RP, et al. Presence and Number of Lymph Node Metastases Are Associated With Compromised Survival for Patients Younger Than Age 45 Years With Papillary Thyroid Cancer. *J Clin Oncol* (2015) 33(21):2370–5. doi: 10.1200/JCO.2014.59.8391
9. Tran Cao HS, Johnston LE, Chang DC, Bouvet M. A critical analysis of the American Joint Committee on Cancer (AJCC) staging system for differentiated thyroid carcinoma in young patients on the basis of the Surveillance, Epidemiology, and End Results (SEER) registry. *Surgery* (2012) 152(2):145–51. doi: 10.1016/j.surg.2012.02.015
10. Olsen KD, DeSanto LW, Pearson BW. Positive Delphian lymph node: clinical significance in laryngeal cancer. *Laryngoscope* (1987) 97(9):1033–7. doi: 10.1288/00005537-198709000-00007
11. Thaler ER, Montone K, Tucker J, Weinstein GS. Delphian lymph node in laryngeal carcinoma: a whole organ study. *Laryngoscope* (1997) 107(3):332–4. doi: 10.1097/00005537-199703000-00010
12. Isaacs JD, Lundgren CI, Sidhu SB, Sywak MS, Edhouse PJ, Delbridge LW. The Delphian lymph node in thyroid cancer. *Ann Surg* (2008) 247(3):477–82. doi: 10.1097/SLA.0b013e31815efdc4
13. Iyer NG, Kumar A, Nixon IJ, Patel SG, Ganly I, Tuttle RM, et al. Incidence and significance of Delphian node metastasis in papillary thyroid cancer. *Ann Surg* (2011) 253(5):988–91. doi: 10.1097/SLA.0b013e31821219ca
14. Zheng G, Zhang H, Hao S, Liu C, Xu J, Ning J, et al. Patterns and clinical significance of cervical lymph node metastasis in papillary thyroid cancer patients with Delphian lymph node metastasis. *Oncotarget* (2017) 8 (34):57089–98. doi: 10.18632/oncotarget.19047
15. saacs JD, McMullen TP, Sidhu SB, Sywak MS, Robinson BG, Delbridge LW. Predictive value of the Delphian and level VI nodes in papillary thyroid cancer. *ANZ J Surg* (2010) 80(11):834–8. doi: 10.1111/j.1445-2197.2010.05334.x
16. Tan Z, Ge MH, Zheng CM, Wang QL, Nie XL, Jiang LH. The significance of Delphian lymph node in papillary thyroid cancer. *Asia Pac J Clin Oncol* (2017) 13(5):e389–e93. doi: 10.1111/ajco.12480
17. Roh JL, Kim JM, Park CI. Central lymph node metastasis of unilateral papillary thyroid carcinoma: patterns and factors predictive of nodal metastasis, morbidity, and recurrence. *Ann Surg Oncol* (2011) 18(8):2245–50. doi: 10.1245/s10434-011-1600-z
18. Roh JL, Kim JM, Park CI. Central cervical nodal metastasis from papillary thyroid microcarcinoma: pattern and factors predictive of nodal metastasis. *Ann Surg Oncol* (2008) 15(9):2482–6. doi: 10.1245/s10434-008-0044-6
19. Roh JL, Kim JM, Park CI. Lateral cervical lymph node metastases from papillary thyroid carcinoma: pattern of nodal metastases and optimal strategy for neck dissection. *Ann Surg Oncol* (2008) 15(4):1177–82. doi: 10.1245/s10434-008-9813-5
20. Huang J, Sun W, Zhang H, Zhang P, Wang Z, Dong W, et al. Use of Delphian lymph node metastasis to predict central and lateral involvement in papillary thyroid carcinoma: A systematic review and meta-analysis. *Clin Endocrinol (Oxf)* (2019) 91(1):170–8. doi: 10.1111/cen.13965
21. Ming Gao MG, Ji Q, Xu Z, Lu H. Ruochuan Cheng, Haixia Guan. Chinese consensus on diagnosis and treatment of thyroid micropapillary carcinoma. *Chin J Clin Oncol* (2016) 43(10):405–11.
22. Association CM. Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Chin J Clin Oncol* (2012) 39(17):1249–72.
23. Alba AC, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ, et al. Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. *JAMA* (2017) 318(14):1377–84. doi: 10.1001/jama.2017.12126. 2656816.
24. Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. *Circulation* (2010) 121(14):1630–6. doi: 10.1161/CIRCULATIONAHA.109.925214
25. Ferlito A, Shaha AR, Rinaldo A. Prognostic value of Delphian lymph node metastasis from laryngeal and hypopharyngeal cancer. *Acta Otolaryngol* (2002) 122(4):456–7. doi: 10.1080/00016480260000201
26. Wierzbicka M, Leszczynska M, Mlodkowska A, Szyfter W, Bartochowska A. The impact of prelaryngeal node metastases on early glottic cancer treatment results. *Eur Arch Otorhinolaryngol* (2012) 269(1):193–9. doi: 10.1007/s00405-011-1747-z
27. Kim WW, Yang SI, Kim JH, Choi YS, Park YH, Kwon SK. Experience and analysis of Delphian lymph node metastasis in patients with papillary thyroid carcinoma. *World J Surg Oncol* (2012) 10:226. doi: 10.1186/1477-7819-10-226
28. Lee YC, Shin SY, Kwon KH, Eun YG. Incidence and clinical characteristics of prelaryngeal lymph node metastasis in papillary thyroid cancer. *Eur Arch Otorhinolaryngol* (2013) 270(9):2547–50. doi: 10.1007/s00405-013-2471-7
29. Oh EM, Chung YS, Lee YD. Clinical significance of Delphian lymph node metastasis in papillary thyroid carcinoma. *World J Surg* (2013) 37(11):2594–9. doi: 10.1007/s00268-013-2157-8
30. Chai YJ, Kim SJ, Choi JY, Koo do H, Lee KE, Youn YK. Papillary thyroid carcinoma located in the isthmus or upper third is associated with Delphian lymph node metastasis. *World J Surg* (2014) 38(6):1306–11. doi: 10.1007/s00268-013-2406-x
31. 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* (2016) 26(1):1–133. doi: 10.1089/thy.2015.0020
32. National Comprehensive Cancer Network I. *2019 Practice Guidelines in Oncology-Thyroid Carcinoma v.2*. National Comprehensive Cancer Network (2019). Available at: www.nccn.org/professionals/physician_gls/PDF/thyroid.pdf.
33. Xingchen Li YD, Liu D, Liu H, Zhou M, Yue K, Shuai Y, et al. Diagnostic model incorporating clinicopathological characteristics of Delphian lymph node metastasis risk profiles in papillary thyroid cancer. (2020). doi: 10.21203/rs.3.rs-42289/v1


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 31 March 2021
doi: 10.3389/fendo.2021.613974

# Nomogram for Preoperative Estimation of Cervical Lymph Node Metastasis Risk in Papillary Thyroid Microcarcinoma

*Jinxiao Sun*[1,2†], *Qi Jiang*[2,3†], *Xian Wang*[2], *Wenhua Liu*[2] *and Xin Wang*[1,2*]

[1] Department of Ultrasonography, Taihu Lake Cadre Sanatorium of Jiangsu Province, Wuxi, China, [2] Department of Ultrasonography, Affiliated Renmin Hospital, Jiangsu University, Zhenjiang, China, [3] Department of Ultrasonography, Yunyang People's Hospital of Danyang, Danyang, China

**Objective:** Accurate preoperative identification of cervical lymph node metastasis (CLNM) is essential for clinical management and established of different surgical protocol for patients with papillary thyroid microcarcinoma (PTMC). Herein, we aimed to develop an ultrasound (US) features and clinical characteristics-based nomogram for preoperative diagnosis of CLNM for PTMC.

**Method:** Our study included 552 patients who were pathologically diagnosed with PTMC between January 2015 and June 2019. All patients underwent total thyroidectomy or lobectomy and divided into two groups: CLNM and non-CLNM. Univariate and multivariate analysis were performed to examine risk factors associated with CLNM. A nomogram comprising the prognostic model to predict the CLNM was established, and internal validation in the cohort was performed.

**Results:** CLNM and non-CLNM were observed in 216(39.1%) and 336(60.9%) cases, respectively. Seven variables of clinical and US features as potential predictors including male sex (odd ratio [OR] = 1.974, 95% confidence interval [CI], 1.243-2.774; P =0.004), age < 45 years (OR = 4.621, 95% CI, 2.160-9.347; P < 0.001), US-reported CLN status (OR = 1.894, 95% CI, 0.754-3.347; P =0.005), multifocality (OR = 1.793, 95% CI, 0.774-2.649; P =0.007), tumor size ≥ 0.6cm (OR = 1.731, 95% CI,0.793-3.852; P =0.018), ETE (OR = 3.772, 95% CI, 1.752-8.441;P< 0.001) and microcalcification (OR = 2.316, 95% CI, 1.099-4.964; P < 0.001) were taken into account. The predictive nomogram was established by involving all the factors above used for preoperative prediction of CLNM in patients with PTCM. The nomogram model showed an AUC of 0.839 and an accuracy of 77.9% in predicting CLNM. Furthermore, the calibration curve demonstrated a strong consistency between nomogram and clinical findings in prediction CLNM for PTMC.

**Conclusions:** The nomogram achieved promising results for predicting preoperative CLNM in PTMC by combining clinical and US risk factor. Our proposed prediction model is able to help determine an individual's risk of CLNM in PTMC, thus facilitate reasonable therapy decision making.

**Keywords: thyroid cancer, microcarcinoma, lymphatic metastasis, nomograms, ultrasound**

OPEN ACCESS

***Edited by:***
*Christoph Reiners, University Hospital Würzburg, Germany*

***Reviewed by:***
*Roberto Vita, University of Messina, Italy*
*Ji Zhang, Taizhou People's Hospital, China*

****Correspondence:***
*Xin Wang*
*15162977621@163.com*

*[†]These authors have contributed equally to this work*

***Specialty section:***
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

***Received:*** *04 October 2020*
***Accepted:*** *03 March 2021*
***Published:*** *31 March 2021*

***Citation:***
*Sun J, Jiang Q, Wang X, Liu W and Wang X (2021) Nomogram for Preoperative Estimation of Cervical Lymph Node Metastasis Risk in Papillary Thyroid Microcarcinoma. Front. Endocrinol. 12:613974. doi: 10.3389/fendo.2021.613974*

## INTRODUCTION

The World Health Organization defines papillary thyroid microcarcinoma (PTMC) as a subset of papillary thyroid carcinoma (PTC), which is ≤1.0 cm at the greatest dimension (1). The incidence of PTC, particularly PTMC, has risen considerably across the world in the past few decades (2). Most of these tumors are not easy to identify clinically because they are not palpable. Thus, the discovery of PTMC can be attributed to the application of routine high-resolution ultrasonography (US), as well as other imaging techniques (3). Despite slow growth and good prognosis are usually observed, some PTMC are accompanied by high-risk features at the time of diagnosis, such as cervical lymph node metastasis (CLNM) and extrathyroidal extension (ETE). This is strongly linked to distant metastasis, high locoregional recurrence, and enhanced death risk (4, 5). Recent evidence indicates a 24-64% incidence of CLNM in PTMC, which usually affects the central neck compartment (6–10).

Patients with PTMC usually undergo central lymph node dissection (CLND) as a standard and necessary procedure when they are suspected of having lymph node involvement in the neck (1). Nevertheless, prophylactic CLND for PTMC is still controversial and uncertain, because prophylactic CLND is expected to enhance therapy-related morbidities like recurrent laryngeal nerve injury, chyle leak, brachial plexus palsy, phrenic nerve palsy, hypoparathyroidism (11). So that, identifying risk factors for CLNM in patients with PTMC before surgery can have a profound impact on the prognosis.

Many studies have reported on the preoperative clinicopathologic risk factors of CLNM for PTMC (3, 6). But the findings have been conflicting (12, 13), and therefore, there has been no agreement on the subject. In addition, only clinicopathologic features were incorporated into the studies (14, 15). As a result, their clinical application is rather limited. Ultrasound (US) examination is a widely applied method for assessing thyroid nodules and cervical lymph node (CLN). The technique has several advantages: radiation-free, convenience, noninvasiveness, inexpensiveness, and real-time. Different from previous studies, our study aimed to establish a simple nomogram based on clinical, haematological and US features to predict the risk of CLNM preoperatively in PTMC. This will enable clinicians to make better clinical decisions and thus improve patient outcomes.

## MATERIALS AND METHODS

### Population

The approval to conduct this retrospective study was provided by the Affiliated Renmin hospital of Jiangsu University. Informed consent requirement was not applicable. Records of 594 patients with surgically confirmed PTMC from January 2015 to June 2019 were retrieved from the hospital's database. All patients had thyroid US examination as part of the presurgical evaluation. After reviewing the records, we excluded 42 patients due to the following reasons: without CLND, history of thyroidectomy, thyroid treatment before US examination, poor-quality US images, distant metastasis, or incomplete medical records. Finally, we included 552 patients in this study.

### US Examination

US was performed using a high-resolution ultrasound scanner (iU22; Philips Healthcare, Eindhoven, the Netherlands) with a 5-12-MHz linear probe by an experienced radiologist. Then, the instrument was operated using a specific "Thyroid" program. Each patient adopted the supine position with the neck fully exposed, and the head lowered and moved slightly backward. Two experienced radiologists independently reviewed the US imaging features of every patient, both of them unaware of sample identity. If the radiologists disagreed, the final decision was made by consensus. Both cross-sectional and longitudinal examinations were conducted to determine the location. The following were the imaging features of each nodule: tumor size (the maximum diameter of the primary lesion), tumor margin, tumor shape, multifocality, bilaterality, aspect ratio (height divided by width on transverse views, A/T), microcalcification, tumor internal echo pattern, ETE and Hashimoto's thyroiditis. Multifocality was considered in cases where one or both lobes exhibited two or more foci. Regarding multifocal PTMC, the largest, dominant tumor was first analyzed. For example, in multifocal cases, tumor size was classified based on the diameter of the largest tumor. The A/T was classified as ≤1 or > 1. Tumor margin was classified as smooth or ill-defined. Tumor shape was classified as either regular or irregular. Internal echo pattern was divided into heterogeneous or homogeneous. Microcalcifications were defined if their largest diameter was ≤ 2 mm (**Figure 1**). Based on the American Joint Committee on Cancer guidelines (16), ETE was defined by at least one of the following US features: thyroid capsule in contact with > 25% of the lesion perimeter, echogenic capsule line loss at the contact site of the lesion, tumor extension past the thyroid capsule, and invasion of the larynx, trachea, esophagus, recurrence laryngeal nerve, common carotid artery, mediastinal vessels, and subcutaneous soft tissues (**Figure 1**). The diagnosis of Hashimoto's thyroiditis (HT) was made based on the US images and thyroid autoantibodies.

In the preoperative evaluation of CLNs, a suspicious lymph node exhibited the following characteristics: internal microcalcifications, hyperechoic change, round shape, vascularity, loss of hilar echogenicity, size > 5 mm, round shape, or necrosis.

The precision of operator-reported imaging features determined the diagnostic performance of our model; as such, we evaluated the interobserver reproducibility of the US features.

### Surgical Treatment

The protocol of thyroid surgery was established as per the guidelines of the American Thyroid Association (2015). Surgeries of ipsilateral lobectomy plus ipsilateral CLND were conducted as initial surgical therapy for PTMC patients with unilateral lesion. Total thyroidectomy plus ipsilateral or bilateral CLND was performed when PTMC lesion with ETE or multifocal carcinomas were restricted to a single lobe. When malignant lesions were found in both lobes of the thyroid, a total

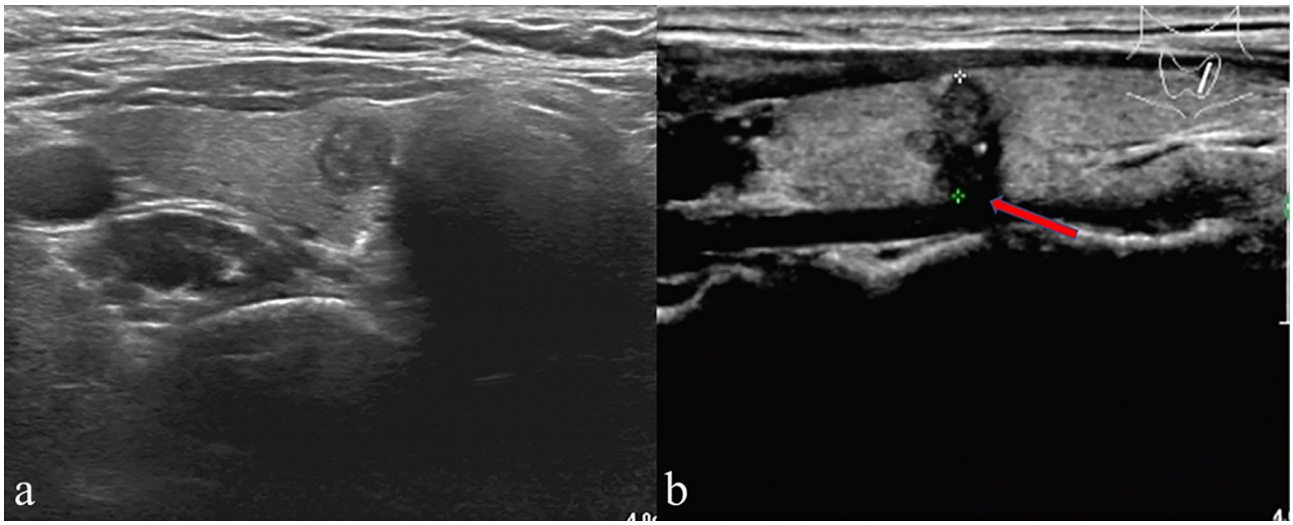


**FIGURE 1** | **(A)** A patient's thyroid ultrasound showed punctated hyperecho in the nodule, indicating the presence of microcalcification. **(B)** A representative patient with ETE showed echogenic capsule line loss at the contact site of the lesion (red arrow) and microcalcification in the nodule.

thyroidectomy plus a bilateral CLND was performed. Lateral lymph node dissection (LLND) was performed only in cases with clinically evident lateral neck lymph node metastasis (LLNM).

## Assessment of Clinical Variables

The clinical variables included age, sex, pre-operative TSH level, pre-operative TGAb level and pre-operative TPOAb level.

## Statistical Analysis

Clinical variables and US features were analyzed using univariate analysis. The R software (version 3.5.1) was used for data analysis. Data on continuous variables were expressed as mean ± standard deviation (SD). Categorical variables involved the number of cases. The importance of variables with CLNM was determined by binary logistic regression. A nomogram was established according to the results the binary logistic regression to evaluate risk of CLNM preoperatively. ROC was employed to quantify the discriminative capability of the nomogram by comparing nomogram-predicted versus the observed CLNM probability. Internally validated was performed by bootstraps with 1,000 resample to assess the accuracy of the constructed logistic regression model. A probability(p) value of 0.05 defined statistical significance.

# RESULTS

## Demographics of PTMC Patients

In total, 552 patients were confirmed by pathological examination of surgical specimens, consisting of 450 (81.5%) women and 102 (18.6%) men. The patients had an average age of 45.5 ± 10.0 (22-75) years. Based on the pathological examination of surgical samples, 216 (39.1%) patients had CLNM, out of which 129 (23.4%) exhibited only central lymph node metastasis. In total, 63 (11.4%) patients had LLNM, whereas 24 (4.3%) patients had LLNM without central lymph node metastasis (leap metastasis). The subjective US-reported CLN status had a low accuracy of 0.677 for the whole cohort. The specificity was high (84.5%) but with low sensitivity (40.3%). A total of 127 patients were reported as LN negative but verified to have CLNM after the operation.

## Comparison Between Metastasis and No Metastasis Groups

The baseline clinical characteristics and US features with versus without CLNM are listed in **Table 1**. The age was significantly younger ($p<0.001$), and the CLNM group had considerably more male patients, relative to the non-CLNM group (27.8% vs. 19.3%, $p=0.009$). Based on US findings, the incidence of multifocality, bilaterality, and ETE was substantially higher in CLNM, relative to non-CLNM ($p= 0.008$, $P=0.002$, and $p< 0.001$, respectively). By contrast, the tumor size was relatively larger in CLNM than in non-CLNM ($p< 0.001$). Additionally, PTMC that had CLNM was more prone to microcalcifications, but no considerable difference was observed in HT rate, location, Pre-operative TSH, Pre-operative TGAb, Pre-operative TPOAb, tumor shape, tumor margin, A/T and internal echo between the two groups. Agreement was satisfactory between the two radiologists for the US features, with kappa coefficients between 0.78 and 0.89.

## Analysis of CLNM Risk Factors

Regarding univariate analysis, sex ($P =0.002$), age ($P < 0.001$), US-reported CLN status ($P < 0.001$), multifocality ($P =0.001$), bilaterality ($P = 0.024$), ETE ($P < 0.001$), tumor size ($P=0.005$) and microcalcifications ($P < 0.001$) are strongly linked to CLNM. Several variables were shown to be substantially related to CLNM

**TABLE 1** | Clinicopathological characteristics and US features associated with CLNM in PTMC patients.

| Variables | CLNM(–) | CLNM(+) | P值 |
|---|---|---|---|
| Sex | | | 0.009 |
| Male | 65 | 60 | |
| Female | 271 | 156 | |
| Age | 51.0 ± 11.0 | 43.6 ± 11.1 | <0.001 |
| <45 | 252 | 105 | <0.001 |
| ≥45~ | 84 | 111 | |
| Location | | | 0.657 |
| Isthmus | 12 | 5 | |
| Upper | 72 | 56 | |
| Middle | 162 | 109 | |
| Lower | 90 | 46 | |
| HT | | | 0.701 |
| Negative | 264 | 162 | |
| Positive | 72 | 54 | |
| US-reported CLN status | | | <0.001 |
| Negative | 284 | 127 | |
| Positive | 52 | 89 | |
| Multifocality | | | 0.008 |
| Negative | 291 | 150 | |
| Positive | 45 | 66 | |
| Bilaterality | | | 0.002 |
| Negative | 306 | 193 | |
| Positive | 30 | 23 | |
| Tumor size(cm) | | | 0.025 |
| <0.6 | 177 | 75 | |
| ≥0.6 | 159 | 141 | |
| Margin | | | |
| Smooth | 84 | 67 | 0.195 |
| Ill-defined | 252 | 149 | |
| Shape | | | |
| Regular | 47 | 37 | 0.676 |
| Irregular | 289 | 179 | |
| Internal echo | | | |
| homogeneous | 35 | 12 | 0.178 |
| heterogeneous | 301 | 204 | |
| A/T | | | 0.941 |
| ≤1 | 177 | 114 | |
| >1 | 159 | 102 | |
| Microcalcification | | | <0.001 |
| Negative | 201 | 66 | |
| Positive | 135 | 150 | |
| ETE | | | <0.001 |
| Negative | 255 | 99 | |
| Positive | 81 | 117 | |
| Pre-operative TSH (mU/L) | | | 0.832 |
| <2.5 | 219 | 135 | |
| ≥2.5 | 117 | 81 | |
| Pre-operative TGAb (kU/L) | | | 0.822 |
| <1 | 210 | 141 | |
| ≥1 | 126 | 75 | |
| Pre-operative TPOAb (kU/L) | | | 0.630 |
| <1 | 156 | 90 | |
| ≥1 | 180 | 126 | |

based on multivariate logistic regression modeling. These included male sex (odd ratio [OR] = 1.974, 95% CI, 1.243-2.774; P =0.004), age < 45 years (OR = 4.621, 95% CI, 2.160-9.347; P < 0.001), US-reported CLN status (OR = 1.894, 95% CI, 0.754-3.347; P =0.005), multifocality (OR = 1.793, 95% CI, 0.774-2.649; P =0.007), tumor size ≥0.6cm (OR = 1.731, 95% CI,0.793-3.852; P =0.018), ETE (OR = 3.772, 95% CI, 1.752-8.441; P < 0.001) and microcalcifications (OR = 2.316, 95% CI, 1.099-4.964; P < 0.001) (**Table 2**).

## Nomogram Construction

**Figure 2** shows a nomogram created from important factors linked to CLNM. The nomogram contained seven risk factors (sex, age, US-reported CLN status, multifocality, tumor size, microcalcification, and ETE) to estimate the metastasis risk of CLNM for PTMC before surgery. Age yields the largest contribution to the prediction model, while ETE provides the next largest contribution. We assigned a score to every level within variables based on the point scale. Subsequently, we determined the risk of CLNM in each subject by summing up all total scores and identifying it on the total point scale. The predictive nomogram was also verified (**Figure 3**, AUC = 0.839,95%CI, 0.741-0.947) with sensitivity, specificity, and accuracy as 0.779, 0.715, and 0.830. The calibration plots exhibited an excellent consistency between the actual metastasis probability of CLN and predicted metastasis probability with additional 1000 bootstraps (**Figure 4**; Mean absolute error = 0.014).

# DISCUSSION

To avoid overdiagnosis and the associated treatment, the guidelines of the American Thyroid Association (2015) recommend that active surveillance should be taken instead of surgical treatment for low-risk PTMC (1). The definition of low-risk PTMC is based on the absence of local invasion or distant metastasis, and convincing cytological evidence (1). Even in developed countries, the management of low-risk PTMC remains unclear (17, 18). This is because some PTMC progress during active surveillance, and are wrongly considered as low-risk (19). The study conducted by Choi et al. (20) showed that active surveillance could lead to poor disease outcomes because of clinically apparent lymph node metastasis. Most studies indicated that CLNM is a crucial recurrence risk factor, but is usually not detected in patients clinically (10, 21, 22). Therefore, identifying predictive factors that are linked to CLNM could guide appropriate surgical approaches for patients. Several previous studies have shown that CLNM prevalence ranged between 24% and 64% (8–10). Herein, the CLNM incidence in PTMC was 39.13%, and this was consistent with previous findings.

In our research, we established and internally validated a prediction model based on clinical and US features for predicting the probability of CLNM in PTMC patients. We have a major difference with other published studies (12, 23) because we evaluated non-invasive and preoperatively the individual probability of CLNM in PTMC. We analyzed the positive CLN involvement correlations between clinical characteristics, US features of primary thyroid lesions, and hemato-immunological parameters. Multivariate analysis revealed that male and young age (<45 years) were independent predictors for CLNM. This was consistent with the present results reported by others in

**TABLE 2** | Univariate and multivariate analysis of 552 PTMC primary sites with clinical and US features for predicting CLNM.

| Independent variable | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| Age(years) | | | | |
| ≥45 | 1(reference) | | 1(reference) | |
| < 45 | 3.171(1.700–6.007) | <0.001 | 4.621 (2.160–9.347) | <0.001 |
| Sex | | | | |
| Female | 1(reference) | | 1(reference) | |
| Male | 2.374(1.243–3.774) | 0.002 | 1.974(1.243–2.774) | 0.004 |
| US-reported CLN status | | | | |
| Negative | 1(reference) | | 1(reference) | |
| Positive | 2.154 (0.995–3.547) | <0.001 | 1.894 (0.754–3.347) | 0.005 |
| Multifocality | | | | |
| Negative | 1(reference) | | 1(reference) | |
| Positive | 2.845(1.369–6.061) | 0.001 | 1.793 (0.774–2.649) | 0.007 |
| Bilaterality | | | | |
| Negative | 1(reference) | | 1(reference) | |
| Positive | 1.372 (1.192–1.594) | 0.024 | 1.074 (0.763-1.402) | 0.763 |
| Tumor size(cm) | | | | |
| <0.6 | 1(reference) | | 1(reference) | |
| ≥0.6 | 2.093(1.144–3.892) | 0.005 | 1.731 (0.793–3.852) | 0.018 |
| Microcalcification | | | | |
| Negative | 1(reference) | | 1(reference) | |
| Positive | 3.384(1.825–6.429) | <0.001 | 2.316 (1.099–4.964) | <0.001 |
| ETE | | | | |
| Negative | 1(reference) | | 1(reference) | |
| Positive | 3.721(1.988–7.092) | <0.001 | 3.772 (1.752–8.441) | <0.001 |

patients with PTMC (24, 25). A higher basal metabolic rate in young male patients might enhance the proliferative and thus metastatic ability of tumor cells, and it will lead to more metastasis (26). Elevated levels of TSH, especially in conjunction with HT, are considered a risk factor for the development of thyroid malignancy and have been associated with a more advanced status of papillary thyroid carcinoma (27). However, the data regarding the impact of TSH and HT on CLNM in PTMC were inconsistent. Some studies have shown more lymph node metastasis in PTMC patients with HT (28), but others less (29). Some previous literatures focusing on PTMC patients found no association between the coexistence of HT and CLNM (30, 31). This is consistent with our study. Currently, ultrasonography is extensively applied in the evaluation of CLNM in PTMC patients, not only at the initial staging, but also in the course of subsequent surveillance after thyroidectomy (12). In our study, US features were the risk factors including US-reported CLN status, tumor size, ETE, multifocality and microcalcification. Tumors that exhibit certain features like a larger size, multifocality, and microcalcification on US examination were strongly linked to CLNM in our research, and similar findings have been reported previously (12, 32–34).

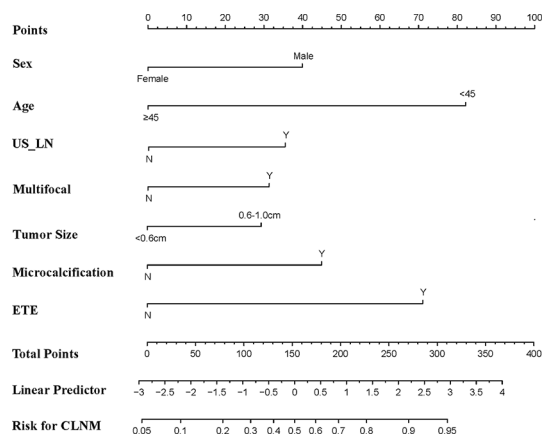


**FIGURE 2** | Nomogram for predicting CLNM in PTMC patients.

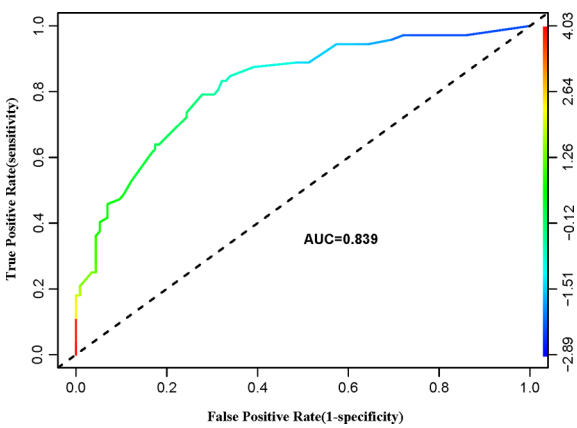


**FIGURE 3** | ROC curve analysis to predict CLNM in PTMC patients.

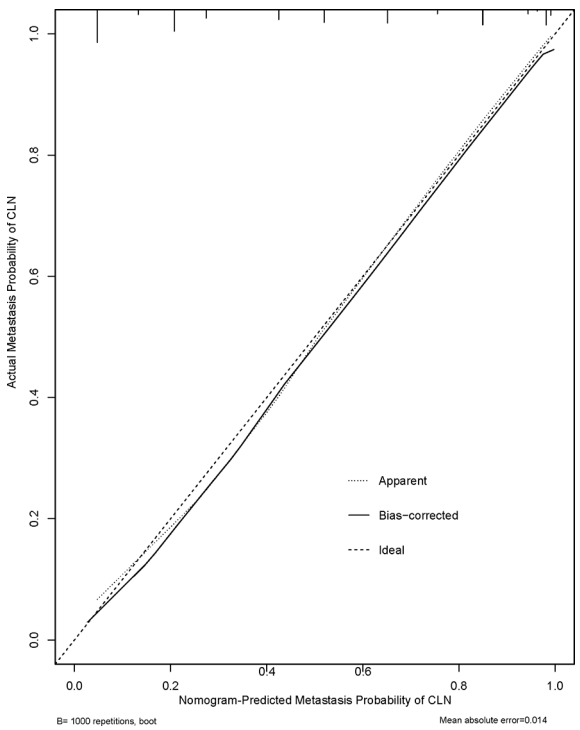


**FIGURE 4** | Calibration curves of the nomogram for predicting CLNM in PTMC patients.

Usually, ETE is a clinicopathological factor associated with CLNM (3, 12, 23, 28). But in our study, ETE was evaluated by US examination, which is determined by the purpose of our study. In addition, some studies have confirmed that US is satisfied with the evaluation of preoperative ETE (35), which provides the possibility for accurate prediction of CLNM before surgery. In our results concerning PTMC, univariate analysis indicated bilaterality as a risk factor for CLNM, however, multivariate analysis showed no statistical significance. The reason may be that multifocality and bilaterality were partially overlapped.

Our study built a predictive nomogram using the predictors identified in the multivariate regression model (**Figure 2**). The nomogram incorporates seven factors to generate a probability of a clinical event that is unique to an individual. This will finally assist clinicians in decision (36). The nomogram showed excellent discriminative capability (0.839, 95%CI, 0.741-0.947). Incorporating the clinical and US features into an easy-to-use nomogram enables preoperative individualized CLNM prediction. The nomogram established herein will help determine the existence of CLNM, which may avoid over-as well as under-treatment. Based on our results, we recommend that PTMC patients at a high risk of CLNM should undergo prophylactic lymph node dissection to prevent reoperations because of recurrence. Meanwhile, patients at low risk of CLNM should not receive prophylactic lymph node dissection because this may lead to unnecessary damage to the neck and possible surgical complications.

This retrospective observational study has some limitations. First, patients were enrolled from a single tertiary medical center, hence there was a potential for selection bias. Errors and biases tend to be higher in retrospective studies than in prospective studies. Second, for multifocal nodules, we only analyzed the largest one, when the information about other nodules was not available. Third, the performance of our nomogram depends on the operators with different levels of experience. The criteria used to evaluate the US signature were subjective. Nonetheless, there was shown to be an excellent interobserver agreement in our study. Finally, the sample size was not sufficiently large. As such, there is a need to conduct further studies involving a larger sample size and evaluation in external datasets to verify these findings.

In summary, we have built a predictive nomogram incorporating two clinical and five US features that can give a precise preoperative estimation of CLNM risk for each PTMC patients. However, further researches that involves larger samples sizes should be conducted to verify our findings.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

JS, XinW, QJ, XiaW, and WL contributed conception and design of the study. XinW supervised the project. QJ and WL organized the database. JS, XinW, QJ, and XiaW acquired, analyzed, and interpreted the patient date. JS and XinW wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

This study was supported in part by a grant-in-aid for scientific research from the Jiangsu Provincial Commission of Health and Family Planning (Grant Nos. ZDXKC2016011), Wuxi Municipal Bureau on Science and Technology (Grant No. CMB41S1701) and Zhenjiang Science and Technology support Plan of Social Development Project (Grant No. SH2020046).

## REFERENCES


1. 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* (2016) 26:1–133.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *Ca: A Cancer J For Clin* (2020) 70:7–30.
3. Kim SK, Park I, Woo JW, Lee JH, Choe JH, Kim JH, et al. Predictive Factors for Lymph Node Metastasis in Papillary Thyroid Microcarcinoma. *Ann Surg Oncol* (2016) 23:2866–73.
4. Lee KJ, Cho YJ, Kim SJ, Lee SC, Kim JG, Ahn CJ, et al. Analysis of the clinicopathologic features of papillary thyroid microcarcinoma based on 7-mm tumor size. *World J Surg* (2011) 35:318–23.
5. Wang K, Xu J, Li S, Liu S, Zhang L. Population-based study evaluating and predicting the probability of death resulting from thyroid cancer among patients with papillary thyroid microcarcinoma. *Cancer Med* (2019) 8:6977–85.
6. Cho SY, Lee TH, Ku YH, Kim HI, Lee GH, Kim MJ. Central lymph node metastasis in papillary thyroid microcarcinoma can be stratified according to the number, the size of metastatic foci, and the presence of desmoplasia. *Surgery* (2015) 157(1):111–8.
7. Zhao Q, Ming J, Liu C, Shi L, Xu X, Nie X, et al. Multifocality and total tumor diameter predict central neck lymph node metastases in papillary thyroid microcarcinoma. *Ann Surg Oncol* (2013) 20(3):746–52.
8. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al. Clinical significance of metastasis to the central compartment from papillary microcarcinoma of the thyroid. *World J Surg* (2006) 30:91–9.
9. Kwak JY, Kim EK, Kim MJ, Son EJ, Chung WY, Park CS, et al. Papillary microcarcinoma of the thyroid: predicting factors of lateral neck node metastasis. *Ann Surg Oncol* (2009) 16:1348–55.
10. Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. *Ann Surg* (2003) 237:399–407.
11. Sancho JJ, Lennard TWJ, Paunovic I, Triponez F, Sitges-Serra A. Prophylactic central neck disection in papillary thyroid cancer: a consensus report of the European Society of Endocrine Surgeons (ESES). *Langenbeck's Arch Surgery* (2014) 399:155–63.
12. Jiwang L, Yahong L, Kai L, Bo H, Yuejiao Z, Haotian W, et al. Clinicopathologic factors and preoperative ultrasonographic characteristics for predicting central lymph node metastasis in papillary thyroid microcarcinoma: a single center retrospective study. *Braz J Otorhinolaryngol* (2020), S1808-8694(20)30062-8. doi: 10.1016/j.bjorl.2020.05.004
13. Feng JW, Pan H, Wang L, Ye J, Jiang Y, Qu Z. Determine the Optimal Extent of Thyroidectomy and Lymphadenectomy for Patients With Papillary Thyroid Microcarcinoma. *Front Endocrinol (Lausanne)* (2019) 10:363.
14. Luo Y, Zhao Y, Chen K, Shen J, Shi J, Lu S, et al. Clinical analysis of cervical lymph node metastasis risk factors in patients with papillary thyroid microcarcinoma. *J Endocrinol Invest* (2019) 42:227–36.
15. Zheng X, Peng C, Gao M, Zhi J, Hou X, Zhao J, et al. Risk factors for cervical lymph node metastasis in papillary thyroid microcarcinoma: a study of 1,587 patients. *Cancer Biol Med* (2019) 16:121–30.
16. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* (2010) 17:1471–4.
17. Sugitani I, Ito Y, Miyauchi A, Imai T, Suzuki S. Active Surveillance Versus Immediate Surgery: Questionnaire Survey on the Current Treatment Strategy for Adult Patients with Low-Risk Papillary Thyroid Microcarcinoma in Japan. *Thyroid* (2019) 29:1563–71.
18. Oh HS, Ha J, Kim HI, Kim TH, Kim WG, Lim DJ, et al. Active Surveillance of Low-Risk Papillary Thyroid Microcarcinoma: A Multi-Center Cohort Study in Korea. *Thyroid* (2018) 28:1587–94.
19. Jeong SY, Baek JH, Choi YJ, Lee JH. Ethanol and thermal ablation for malignant thyroid tumours. *Int J Hyperthermia* (2017) 33:938–45.
20. Choi JB, Lee WK, Lee SG, Ryu H, Lee CR, Kang SW, et al. Long-term oncologic outcomes of papillary thyroid microcarcinoma according to the presence of clinically apparent lymph node metastasis: a large retrospective analysis of 5,348 patients. *Cancer Manag Res* (2018) 10:2883–91.
21. Hay ID, Hutchinson ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS, et al. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. *Surgery* (2008) 144:980–7. discussion 987-988.
22. Chow SM, Law SC, Chan JK, Au SK, Yau S, Lau WH. Papillary microcarcinoma of the thyroid-Prognostic significance of lymph node metastasis and multifocality. *Cancer* (2003) 98:31–40.
23. Wang Y, Guan Q, Xiang J. Nomogram for predicting central lymph node metastasis in papillary thyroid microcarcinoma: A retrospective cohort study of 8668 patients. *Int J Surg* (2018) 55:98–102.
24. Zhang L, Wei WJ, Ji QH, Zhu YX, Wang ZY, Wang Y, et al. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. *J Clin Endocrinol Metab* (2012) 97:1250–7.
25. Qu N, Zhang L, Ji QH, Chen JY, Zhu YX, Cao YM, et al. Risk Factors for Central Compartment Lymph Node Metastasis in Papillary Thyroid Microcarcinoma: A Meta-Analysis. *World J Surg* (2015) 39:2459–70.
26. Rahbari R, Zhang L, Kebebew E. Thyroid cancer gender disparity. *Future Oncol* (2010) 6:1771–9.
27. Nagayama Y. Thyroid Autoimmunity and Thyroid Cancer - The Pathogenic Connection: A 2018 Update. *Horm Metab Res* (2018) 50:922–31.
28. Zhang C, Li BJ, Liu Z, Wang LL, Cheng W. Predicting the factors associated with central lymph node metastasis in clinical node-negative (cN0) papillary thyroid microcarcinoma. *Eur Arch Otorhinolaryngol* (2020) 277:1191–8.
29. Zhu F, Shen YB, Li FQ, Fang Y, Hu L, Wu YJ. The Effects of Hashimoto Thyroiditis on Lymph Node Metastases in Unifocal and Multifocal Papillary Thyroid Carcinoma: A Retrospective Chinese Cohort Study. *Med (Baltimore)* (2016) 95:e2674.
30. Kim KE, Kim EK, Yoon JH, Han KH, Moon HJ, Kwak JY. Preoperative prediction of central lymph node metastasis in thyroid papillary microcarcinoma using clinicopathologic and sonographic features. *World J Surg* (2013) 37:385–91.
31. Song J, Yan T, Qiu W, Fan Y, Yang Z. Clinical Analysis of Risk Factors for Cervical Lymph Node Metastasis in Papillary Thyroid Microcarcinoma: A Retrospective Study of 3686 Patients. *Cancer Manag Res* (2020) 12:2523–30.
32. Guo JN, Song LH, Yu PY, Yu SY, Deng SH, Mao XH, et al. Ultrasound Elastic Parameters Predict Central Lymph Node Metastasis of Papillary Thyroid Carcinoma. *J Surg Res* (2020) 253:69–78.
33. Oh EM, Chung YS, Song WJ, Lee YD. The pattern and significance of the calcifications of papillary thyroid microcarcinoma presented in preoperative neck ultrasonography. *Ann Surg Treat Res* (2014) 86:115–21.
34. Tian X, Song Q, Xie F, Ren L, Zhang Y, Tang J, et al. Papillary thyroid carcinoma: an ultrasound-based nomogram improves the prediction of lymph node metastases in the central compartment. *Eur Radiol* (2020) 30(11):5881–93. doi: 10.1007/s00330-020-06906-6
35. Hu S, Zhang H, Sun Z, Ge Y, Li J, Yu C, et al. Preoperative assessment of extrathyroidal extension of papillary thyroid carcinomas by ultrasound and magnetic resonance imaging: a comparative study. *Radiol Med* (2020) 125:870–6.
36. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. *Lancet Oncol* (2015) 16:e173–180.


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 28 April 2021
doi: 10.3389/fendo.2021.666315

# A Nomogram Based on Clinical and Ultrasound Characteristics to Predict Central Lymph Node Metastasis of Papillary Thyroid Carcinoma

*Jia-Wei Feng, Li-Zhao Hong, Fei Wang, Wan-Xiao Wu, Jun Hu, Sheng-Yong Liu, Yong Jiang* and Jing Ye**

*Department of Thyroid Surgery, The Third Affiliated Hospital of Soochow University, Changzhou First People's Hospital, Changzhou, China*

OPEN ACCESS

**Edited by:**
*Christoph Reiners, University Hospital Würzburg, Germany*

**Reviewed by:**
*Jeffrey A. Knauf, Cleveland Clinic, United States*
*Chiara Mele, Università del Piemonte Orientale, Italy*
*Nicolas Schlegel, Julius Maximilian University of Würzburg, Germany*

***Correspondence:**
*Yong Jiang*
*yjiang8888@hotmail.com*
*Jing Ye*
*gif55171@163.com*

**Specialty section:**
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

**Received:** *10 February 2021*
**Accepted:** *29 March 2021*
**Published:** *28 April 2021*

**Citation:**
*Feng J-W, Hong L-Z, Wang F, Wu W-X, Hu J, Liu S-Y, Jiang Y and Ye J (2021) A Nomogram Based on Clinical and Ultrasound Characteristics to Predict Central Lymph Node Metastasis of Papillary Thyroid Carcinoma. Front. Endocrinol. 12:666315. doi: 10.3389/fendo.2021.666315*

**Background:** The status of lymph nodes in the central compartment is crucial to determining the surgical strategies for papillary thyroid carcinoma (PTC). We aimed to develop a nomogram for predicting central lymph node metastasis (CLNM).

**Methods:** A total of 886 PTC patients who underwent total thyroidectomy or lobectomy with central neck dissection (CND) from July 2019 to June 2020 were retrospectively retrieved. Clinical and ultrasound features were collected. Univariate and multivariate analysis were performed to determine risk factors of CLNM. A nomogram for predicting CLNM was developed, internal and external calibration was performed for the established model.

**Results:** Variables (sex, chronic lymphocytic thyroiditis, tumor size, the number of foci, tumor location, margin) significantly associated with CLNM were included in the nomogram. The nomogram showed excellent calibration in the training group and validation group, with area under curves of 0.806 (95% CI, 0.771 to 0.825), and 0.799 (95% CI, 0.778–0.813) respectively.

**Conclusion:** Through this accurate and easy-to-use nomogram, the possibility of CLNM can be objectively quantified preoperatively. Clinicians can use this nomogram to evaluate the status of lymph nodes in PTC patients and consider prophylactic CND for those with high scores.

**Keywords: papillary thyroid carcinoma, central lymph node metastasis, central neck dissection, nomogram, surgery**

## INTRODUCTION

The incidence of thyroid cancer is rising worldwide, and more than 90% of all thyroid cancers are differentiated thyroid cancer (DTC) (1). Papillary thyroid carcinoma (PTC) is the most common type of DTC, and tends to metastasize to cervical lymph nodes. Central compartment lymph nodes are the first to be involved in PTC. According to the American Thyroid Association Surgery Working Group, the central compartment refers to level VI. The VI region extends from the lower

edge of the hyoid to the upper edge of the sternum, and the bilateral boundary is the bilateral common carotid artery. The central neck compartment is subdivided into four zones for the dissection: prelaryngeal (delphian), pretracheal, right and left paratracheal regions. As reported, the risk of lymph node metastasis (LNM) in the central neck compartment was the highest, ranging from 18% to 80% (2–4). Some studies reported that central lymph node metastasis (CLNM) was even associated with an increased risk of regional recurrence (5, 6).

Preoperative detection techniques such as high-resolution ultrasonography (US) and US-guided fine-needle aspiration (FNA) biopsy can greatly improve the diagnosis of PTC. However, due to the limitations of imaging technology, the detection rate of CLNM is relatively low before surgery. For example, the diagnostic sensitivity of US for CLNM is only 51% to 58.3%, and the false negative rate is as high as 44.6% (7, 8). Currently, there is no uniform standard to measure the advantages and disadvantages of routine central neck dissection (CND). Hence, there has been controversy about the role of routine CND. Under these circumstances, an appropriate and noninvasive tool that could quantify the risk of CLNM may be helpful for the optimal treatment of PTC patients.

Different from previous studies that only determine the risk factors of CLNM, we aimed not only to identify risk factors for predicting CLNM, but also to develop and validate the nomogram *via* clinical and US variables. Through this accurate and easy-to-use nomogram, which has excellent user-friendliness and convenience in formulating personalized treatments for patients, the possibility of CLNM can be objectively quantified preoperatively.

# MATERIALS AND METHODS

## Patients

The study was approved by the Institutional Review Board of Changzhou First People's Hospital. All participants gave written informed consent for their clinical records to be used in this study. The records of patients with PTC who underwent surgery from July 2019 to June 2020 at the Department of Thyroid Surgery of Changzhou First People's Hospital were retrospectively reviewed. Patients were excluded from the study if they have any of the following factors: (1) non-PTCs (medullary/follicular/anaplastic) or other subtypes than classic PTC (such as mixed PTC and so on); (2) patients who underwent non-curable surgery or did not undergo CND; (3) patients with another malignancy before thyroidectomy; (4) patients with previous thyroid operation; (5) distant metastasis at diagnosis on pathological or clinical analysis; (6) history of neck radiation or familial cancer; (7) incomplete clinical data or missing follow-up. According to above criteria, 886 patients with PTC were enrolled in this study. **Figure 1** showed the flow chart of the patients enrolled in our study.

## Preoperative Examination and Surgical Procedures

With the discovery of thyroid nodule(s), a complete examination would be carried out. Apart from the routine measurement of thyroid hormone levels, US of the neck would be used to evaluate the primary lesions and cervical lymph nodes. We routinely

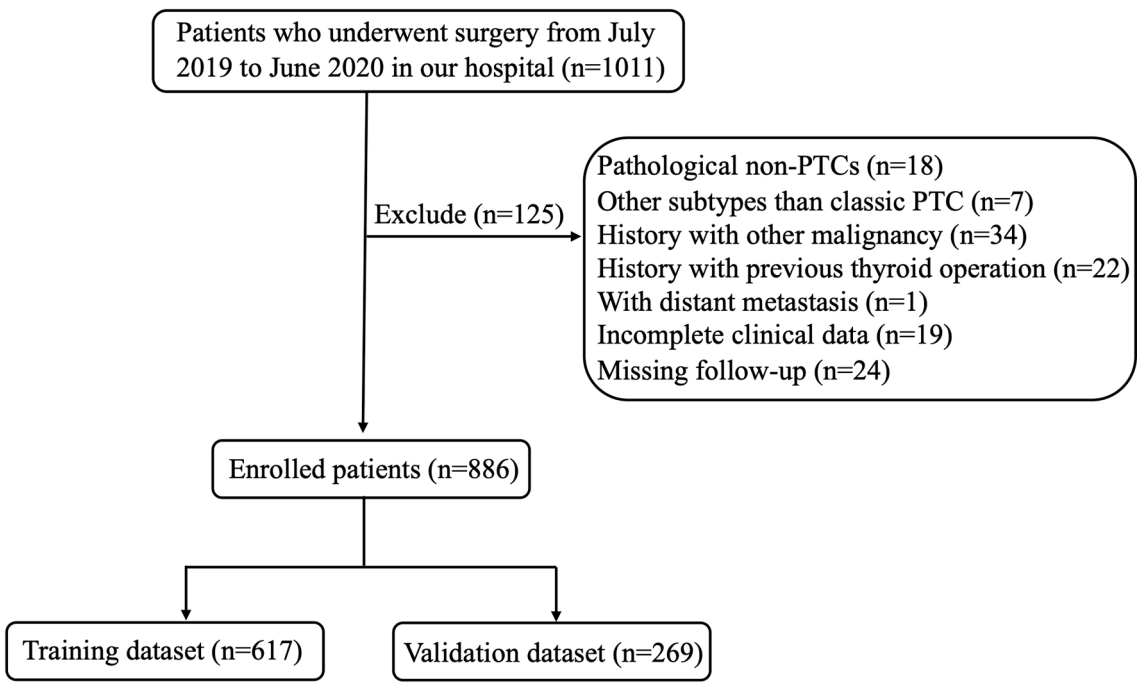


**FIGURE 1** | Flow chart of the patients enrolled in our study.

conducted FNA to confirm the histopathologic diagnosis before surgery. The BRAF V600E mutation, which could help to diagnosis PTC, was also performed. Preoperative US characteristics of each nodule included the following features: aspect ratio (height divided by width on transverse views, A/T), tumor site (upper pole, upper part of the high plane of the isthmus; middle pole, parallel to the isthmus; and lower pole, lower part of the low plane of the isthmus), nodular composition (cystic or spongiform; mixed cystic and solid; solid), echogenicity (anechoic; hyperechoic or isoechoic; hypoechoic; very hypoechoic), margin (smooth; lobulated or irregular; extrathyroidal extension (ETE)), echogenic foci (none or large comet-tail artifacts; macrocalcifications; peripheral calcifications; punctate echogenic foci). Cervical lymph nodes were considered suspicious if they had one of the following characteristics: hyperechoic change, a round shape or necrosis, loss of the fatty hilum, microcalcifications.

Combined with FNA or imaging diagnosis, if patients have any of the following factors (tumor located in the thyroid isthmus, bilateral multifocality, tumor size >4.0 cm, or 1cm< tumor size ≤4.0 cm with risk factors of recurrence, presence of ETE), they would undergo the total thyroidectomy (TT). Otherwise, they would only undergo the lobectomy (9). CND was routinely performed in our institution. Bilateral CND was performed during TT, and ipsilateral CND was performed during lobectomy. TT was defined as the removal of two lobes, the isthmus, and the pyramidal lobe. Lobectomy was defined as the removal of the involved lobe, with the isthmus and the pyramidal lobe. The central compartment refers to level VI. Ipsilateral CND included the removal of prelaryngeal, pretracheal and ipsilateral paratracheal lymph nodes, whereas bilateral CND included the removal of prelaryngeal, pretracheal and bilateral paratracheal lymph nodes (10). All specimens were sent to the department of pathology for paraffin fixation and histological analysis.

## Pathological Examination

All pathology specimens were reviewed and cross-checked by two or more experienced pathologists microscopically. Two or more PTC foci within the thyroid was defined as multifocality. Two or more PTC foci in a single lobe were unilateral multifocality, while 2 or more PTC foci in both lobes or one lobe plus isthmus were bilateral multifocality. The diameter of the largest tumor focus was taken as the primary tumor size in multifocal tumors. Papillary thyroid microcarcinoma (PTMC) was defined as PTC ≤1.0 cm in its maximum diameter while macro-PTC was PTC >1.0 cm in its maximum diameter. The location of the tumor was determined by the largest dominant lesion when the patient had multifocal lesions. The location of the tumor was determined by the portion containing more than two-thirds of the tumor volume when the dominant lesion occupied 2 adjacent parts. We used a holistic definition of chronic lymphocytic thyroiditis (CLT) that included (i) elevated antibodies to thyroid peroxidase level, and/or (ii) findings of diffuse heterogeneity on US, and/or (iii) diffuse lymphocytic thyroiditis on histopathology to avoid selection bias (11).

## Statistical Analyses

All statistical analyses were performed using the SPSS v 25.0 software (Chicago, IL, USA), and R software version 3.5.3 (The R Foundation for Statistical Computing). Continuous variables were expressed as the means ± standard deviations (SD), categorical variables were reported as numbers and percentages. Patients were divided to a "training group" and "validation group" randomly. A t-test, Pearson's chi-square test or Fisher's exact test was used to compare the baseline characteristics of these two groups. Variables with a $P<0.05$ in the univariate analysis were included in the multivariate analysis, which were performed logistic regression analysis to assess risk factors for CLNM in PTC Patients. Variables with a $P<0.05$ in the multivariate analysis were then used to construct a risk prediction model – Nomogram, in R software. We used the receiver operating characteristic (ROC) curve to test the discriminative power and consensus of our established prediction model. The performance of the nomogram was further evaluated by the calibration chart, which plotted the predicted probability of the nomogram against the observed probability. According to our nomogram, the possibility of CLNM was quantified as a risk score, and each patient was divided into different subgroups through the calculated CLNM risk score. When there were total statistical differences between groups, Pearson's chi-square test or Fisher's exact test was used for pairwise comparison, and the $P$ value of pairwise comparison was corrected by Bonferroni method.

# RESULTS

## Baseline Clinical and US Characteristics of Patients With PTC

As summarized in **Table 1**, a total of 886 PTC patients including 205 males (23.1%) and 681 females (76.9%) underwent thyroidectomy plus CND in our institution. The average age at diagnosis was 43.4 ± 12.1 years (range from 23 to 77 years), the average BMI was 24.2 ± 4.57 kg/m$^2$ (range from 11.13 to 38.67 kg/m$^2$), and the average tumor size was 1.21 ± 0.92 cm (range from 0.11 to 8.53 cm). Diabetes was present in 59 patients (6.7%), and CLT was present in 274 patients (30.9%). A total of 714 patients (80.6%) were positive for BRAF V600E mutation, and 172 patients (19.4%) tested negative. Six hundred patients (67.7%) had solitary lesion, 184 patients (20.8%) had 2 foci, and 102 patients (11.5%) had 3 or more than 3 foci. Among 286 patients with multifocal lesions, 182 (20.5%) were confirmed to have bilateral multifocality, 104 (11.7%) were confirmed to have unilateral multifocality. Tumors located in the upper portion of the thyroid gland were detected in 296 (33.4%) patients, and tumors located in the middle/lower lobe of thyroid were detected in 590 (66.6%) patients. The detailed description of the tumor by US was shown in **Table 1**. There were 248 patients (28.0%) suspected of CLNM before surgery by US. And 437 (49.3%) were pathologically confirmed to have CLNM. The average number of removed lymph nodes in the central compartment was 7.8 ± 4.9 (range from 2 to 35); and the average number of metastatic lymph nodes was 2.6 ± 1.6 (range from 0 to 15). There were 737 patients (83.2%) with 6 or more lymph nodes removed during

**TABLE 1 |** Baseline clinical and US imaging characteristics of patients with PTC.

| Characteristics | Total n = 886 | Training dataset n = 617 | Validation dataset n = 269 | *P* value |
|---|---|---|---|---|
| Sex | | | | |
| Male | 205 (23.1%) | 138 (22.4%) | 67 (24.9%) | |
| Female | 681 (76.9%) | 479 (77.6%) | 202 (75.1%) | 0.410 |
| Age (Y) | | | | |
| Mean ± SD (range) | 43.4 ± 12.1 (23–77) | 43.5 ± 12.1 (25–77) | 43.2 ± 11.9 (23–76) | 0.994 |
| ≥55 | 151 (17.0%) | 106 (17.2%) | 45 (16.7%) | |
| <55 | 735 (83.0%) | 511 (82.8%) | 224 (83.3%) | 0.870 |
| BMI ($kg/m^2$) | | | | |
| Mean ± SD (range) | 24.2 ± 4.57 (11.13–38.67) | 24.10 ± 4.62 (13.13–37.27) | 24.41 ± 4.47 (11.13–38.67) | 0.930 |
| Normal | 481 (54.3%) | 342 (55.4%) | 139 (51.7%) | |
| Overweight | 405 (45.7%) | 275 (44.6%) | 130 (48.3%) | 0.302 |
| Diabetes | | | | |
| Absence | 827 (93.3%) | 575 (93.2%) | 252 (93.7%) | |
| Presence | 59 (6.7%) | 42 (6.8%) | 17 (6.3%) | 0.789 |
| BRAF V600E mutation | | | | |
| Negative | 172 (19.4%) | 125 (20.3%) | 47 (17.5%) | |
| Positive | 714 (80.6%) | 492 (79.7%) | 222 (82.5%) | 0.335 |
| CLT | | | | |
| Absence | 612 (69.1%) | 434 (70.3%) | 178 (66.2%) | |
| Presence | 274 (30.9%) | 183 (29.7%) | 91 (33.8%) | 0.217 |
| Maximum tumor size (cm) | | | | |
| Mean ± SD (range) | 1.21 ± 0.92 (0.11–8.53) | 1.31 ± 1.10 (0.11–8.53) | 1.23 ± 0.92 (0.12–7.90) | 0.134 |
| ≤1 | 505 (57.0%) | 348 (56.4%) | 157 (58.4%) | |
| >1 to ≤2 | 255 (28.8%) | 178 (28.8%) | 77 (28.6%) | |
| >2 to ≤4 | 103 (11.6%) | 74 (12.0%) | 29 (10.8%) | |
| >4 | 23 (2.6%) | 17 (2.8%) | 6 (2.2%) | 0.904 |
| The number of foci | | | | |
| 1 | 600 (67.7%) | 416 (67.4%) | 184 (68.4%) | |
| 2 | 184 (20.8%) | 129 (20.9%) | 55 (20.4%) | |
| 3 or more | 102 (11.5%) | 72 (11.7%) | 30 (11.2%) | 0.956 |
| Multifocality | | | | |
| Solitary | 600 (67.7%) | 416 (67.4%) | 184 (68.4%) | |
| Unilateral multifocality | 104 (11.7%) | 81 (13.1%) | 23 (8.6%) | |
| Bilateral multifocality | 182 (20.5%) | 120 (19.4%) | 62 (23.0%) | 0.103 |
| Location | | | | |
| Upper | 296 (33.4%) | 203 (32.9%) | 93 (34.6%) | |
| Middle/Lower | 590 (66.6%) | 414 (67.1%) | 176 (65.4%) | 0.628 |
| Nodular composition | | | | |
| Cystic or spongiform | 2 (0.2%) | 1 (0.2%) | 1 (0.4%) | |
| Mixed cystic and solid | 12 (1.4%) | 9 (1.5%) | 3 (1.1%) | |
| Solid | 872 (98.4%) | 607 (98.4%) | 265 (98.5%) | 0.777 |
| Echogenicity | | | | |
| Anechoic | 3 (0.3%) | 2 (0.3%) | 1 (0.4%) | |
| Hyperechoic or isoechoic | 45 (5.1%) | 30 (4.9%) | 15 (5.6%) | |
| Hypoechoic | 816 (92.1%) | 570 (92.4%) | 246 (91.4%) | |
| Very hypoechoic | 22 (2.5%) | 15 (2.4%) | 7 (2.6%) | 0.971 |
| A/T | | | | |
| ≤1 | 340 (38.4%) | 237 (38.4%) | 103 (38.3%) | |
| >1 | 546 (61.6%) | 380 (61.6%) | 166 (61.7%) | 0.973 |
| Margin | | | | |
| Smooth | 561 (63.3%) | 400 (64.8%) | 161 (59.9%) | |
| Lobulated or irregular | 286 (32.3%) | 193 (31.3%) | 93 (34.6%) | |
| ETE | 39 (4.4%) | 24 (3.9%) | 15 (5.6%) | 0.276 |
| Echogenic foci | | | | |
| None or large comet-tail artifacts | 320 (36.1%) | 221 (35.8%) | 99 (36.8%) | |
| Macrocalcifications | 45 (5.1%) | 33 (5.3%) | 12 (4.5%) | |
| Peripheral calcifications | 12 (1.4%) | 9 (1.5%) | 3 (1.1%) | |
| Punctate echogenic foci | 509 (57.4%) | 354 (57.4%) | 155 (57.6%) | 0.915 |
| US-reported LN status | | | | |
| Negative | 638 (72.0%) | 433 (70.2%) | 205 (76.2%) | |
| Positive | 248 (28.0%) | 184 (29.8%) | 64 (23.8%) | 0.066 |
| CLNM | | | | |

*(Continued)*

**TABLE 1** | Continued

| Characteristics | Total n = 886 | Training dataset n = 617 | Validation dataset n = 269 | *P* value |
|---|---|---|---|---|
| Negative | 449 (50.7%) | 311 (50.4%) | 138 (51.3%) | |
| Positive | 437 (49.3%) | 306 (49.6%) | 131 (48.7%) | 0.806 |
| No. of removed LNs in CC | | | | |
| Mean ± SD (range) | 7.8 ± 4.9 (2–35) | 7.8 ± 4.9 (3–35) | 7.7 ± 5.0 (2–32) | 0.848 |
| ≥6 | 737 (83.2%) | 516 (83.6%) | 221 (82.2%) | |
| <6 | 149 (16.8%) | 101 (16.4%) | 48 (17.8%) | 0.590 |
| No. of metastatic LNs in CC, Mean ± SD (range) | 2.6 ± 1.6 (0–15) | 2.6 ± 1.7 (0–12) | 2.5 ± 1.6 (0–15) | 0.364 |

*US, Ultrasound; PTC, papillary thyroid carcinoma; Y, year; SD, standard deviation; BMI, body mass index; CLT, chronic lymphocytic thyroiditis; ETE, extrathyroidal extension; LN, lymph node; CLNM, central lymph node metastasis; CC, central compartment.*

the operation and 149 patients (16.8%) with less than 6 lymph nodes removed during the operation.

There were 617 patients in the training dataset and 269 patients in the validation dataset. The training and validation groups had no significant differences in clinicopathological characteristics and US features of thyroid nodules ($P$>0.05 for all comparisons), which justified their use as training and validation cohorts.

## Clinical and US Factors Associated With CLNM in the Training Group

In the univariate analysis, CLNM presented the significant association with sex, CLT, tumor size, multifocality, the number of foci, tumor location, A/T, margin, echogenic foci (all $P$<0.05) (**Table 2**). We further conducted the multivariate logistic regression modeling to screen for significant variables associated with CLNM.

Multivariate analysis showed that male (OR: 2.735, 95% CI: 1.716–4.416, $P$<0.001), absence of CLT (OR: 1.877, 95% CI: 1.236–2.853, $P$=0.003), tumor size ranging between 1.0 and 2.0 cm (OR: 2.357, 95% CI: 1.866–4.403, $P$<0.001), tumor size ranging between 2.0 and 4.0 cm (OR: 3.999, 95% CI: 2.735–5.847, $P$<0.001), tumor size > 4.0 cm (OR: 5.342, 95% CI: 1.424–20.043, $P$=0.013), two tumor foci (OR: 1.628, 95% CI: 1.196–3.106, $P$=0.007), three or more tumor foci (OR: 2.924, 95% CI: 1.564–5.468, $P$=0.001), tumors located in the middle/lower pole (OR: 3.604, 95% CI: 2.309–5.625, $P$<0.001), lobulated or irregular margin (OR: 1.704, 95% CI: 1.205–2.410, $P$=0.003), and ETE (OR: 2.330, 95% CI: 1.612–3.973, $P$<0.001) remained independent predictive variables of CLNM, as shown in **Table 2**.

## Development of the Nomogram for Predicting CLNM in PTC Patients

All risk factors that showed statistical significance in the logistic regression model were included in the nomogram, which could help estimate the metastasis risk of central compartment for individual patients with PTC (**Figure 2**). Each variable was proportionally assigned as the point on a scale from 0 to 100 in the nomogram based on the regression coefficient for CLNM. The nomogram confirmed tumor size as the largest contributor to scores. Detailed scores were listed in the **Table 2**. By adding the total score and positioning it on the scale of the total score, the corresponding probability of CLNM in each person can be determined.

## Validation of the Prediction Nomogram

We then performed ROC analysis for the training and validation groups using this model (**Figures 3A, B**). The area under the curves (AUCs) in the training group and validation group were 0.806 (95% CI, 0.771 to 0.825), and 0.799 (95% CI, 0.778–0.813) respectively. Moreover, we calculated the AUC for preoperative US of predicting CLNM (**Figure 3C**). And the AUC was 0.558 (95% CI, 0.542–0.573) only, which was smaller than that of nomogram ($P$<0.001).

Furthermore, we used the similar bootstrap resampling procedure to conduct the internal and external calibration plot for the established model. Predicted and observed metastasis risks of CLNM were in good agreement. Moreover, the corrected risks also showed excellent agreement with observed metastasis risk after the adjustment for optimism, and only minor discrepancies were observed (**Figures 4A, B**).

## Novel Risk Stratification Based on the Predictive Nomogram

Considering that each variable contained in the nomogram has its corresponding risk point, and the total risk score calculated for all patients can quantitatively predict their respective CNM risk, we thereby determined three cut-off values (50, 100, 150) by using recursive partition analysis. As shown in **Table 3**, we established four subgroups as follows: (1) extreme low-risk group (patients with the nomogram score of ≤ 50), (2) low-risk group (50 < risk score ≤ 100), (3) moderate-risk group (100 < risk score ≤ 150), and (4) high-risk group (patients with the score of >150). In the training group, the rates of CLNM for extreme low, low, moderate, and high-risk groups were 12.6%, 29.7%, 62.1%, and 82.9%, respectively ($P$<0.001). Similarly, in the validation group, the rates of CLNM for extreme low, low, moderate, and high-risk groups were 12.0%, 31.6%, 60.3%, and 83.6%, respectively ($P$<0.001). We further studied whether the relative risk for CLNM in each risk category identified by the nomogram were significantly different from each other. After paired comparison, we found there were significant differences between all groups.

# DISCUSSION

With the increasing incidence of thyroid cancer, surgical resection is generally considered to be the most effective treatment for PTC.

**TABLE 2 |** Univariate analysis and multivariate analysis of factors associated with CLNM in the training dataset and score.

| Characteristics | CLNM, No. (%) | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Presence (n = 306) | Absence(n = 311) | *P* value | Adjusted OR (95% CI) | *P* value | Score |
| Sex | | | | | | |
| Female | 212 (69.3%) | 267 (85.9%) | | 1 | | 0 |
| Male | 94 (30.7%) | 44 (14.1%) | <0.001 | 2.753 (1.716–4.416) | <0.001 | 43 |
| Age (Y) | | | | | | |
| ≥55 | 57 (18.6%) | 49 (15.8%) | | | | |
| <55 | 249 (81.4%) | 262 (84.2%) | 0.344 | | | |
| BMI (kg/m$^2$) | | | | | | |
| Normal | 165 (53.9%) | 177 (56.9%) | | | | |
| Overweight | 141 (46.1%) | 134 (43.1%) | 0.455 | | | |
| Diabetes | | | | | | |
| Absence | 288 (94.1%) | 287 (92.3%) | | | | |
| Presence | 18 (5.9%) | 24 (7.7%) | 0.366 | | | |
| BRAF V600E mutation | | | | | | |
| Negative | 66 (21.6%) | 59 (19.0%) | | | | |
| Positive | 240 (78.4%) | 252 (81.0%) | 0.422 | | | |
| CLT | | | | | | |
| Presence | 70 (22.9%) | 113 (36.3%) | | 1 | | 0 |
| Absence | 236 (77.1%) | 198 (63.7%) | <0.001 | 1.877 (1.236–2.853) | 0.003 | 24 |
| Maximum tumor size (cm) | | | | | | |
| ≤1 | 124 (40.5%) | 224 (72.0%) | | 1 | | 0 |
| >1 to ≤2 | 116 (37.9%) | 62 (19.9%) | | 2.357 (1.866–4.403) | <0.001 | 33 |
| >2 to ≤4 | 52 (17.0%) | 22 (7.1%) | | 3.999 (2.735–5.847) | <0.001 | 67 |
| >4 | 14 (4.6%) | 3 (1.0%) | <0.001 | 5.342 (1.424–20.043) | 0.013 | 100 |
| The number of foci | | | | | | |
| 1 | 171 (55.9%) | 245 (78.8%) | | 1 | | 0 |
| 2 | 83 (27.1%) | 46 (14.8%) | | 1.628 (1.196–3.106) | 0.007 | 27 |
| 3 or more | 52 (17.0%) | 20 (6.4%) | <0.001 | 2.924 (1.564–5.468) | 0.001 | 54 |
| Multifocality | | | | | | |
| Solitary | 171 (55.9%) | 245 (78.8%) | | 1 | | |
| Unilateral multifocality | 58 (19.0%) | 23 (7.4%) | | 1.341 (0.638–2.816) | 0.439 | |
| Bilateral multifocality | 77 (25.2%) | 43 (13.8%) | <0.001 | 4.610 (3.178–6.688) | 0.344 | |
| Location | | | | | | |
| Upper | 52 (17.0%) | 151 (48.6%) | | 1 | | 0 |
| Middle/Lower | 254 (83.0%) | 160 (51.4%) | <0.001 | 3.604 (2.309–5.625) | <0.001 | 65 |
| Nodular composition | | | | | | |
| Cystic or spongiform | 0 (0.0%) | 1 (0.3%) | | | | |
| Mixed cystic and solid | 6 (2.0%) | 3 (1.0%) | | | | |
| Solid | 300 (98.0%) | 307 (98.7%) | 0.294 | | | |
| Echogenicity | | | | | | |
| Anechoic | 2 (0.7%) | 0 (0.0%) | | | | |
| Hyperechoic or isoechoic | 19 (6.2%) | 11 (3.5%) | | | | |
| Hypoechoic | 278 (90.8%) | 292 (93.9%) | | | | |
| Very hypoechoic | 7 (2.3%) | 8 (2.6%) | 0.151 | | | |
| A/T | | | | | | |
| ≤1 | 145 (47.4%) | 92 (29.6%) | | 1 | | |
| >1 | 161 (52.6%) | 219 (70.4%) | <0.001 | 1.343 (0.892–2.021) | 0.158 | |
| Margin | | | | | | |
| Smooth | 175 (57.2%) | 225 (72.3%) | | 1 | | 0 |
| Lobulated or irregular | 110 (35.9%) | 83 (26.7%) | | 1.704 (1.205–2.410) | 0.003 | 21 |
| ETE | 21 (6.9%) | 2 (1.0%) | <0.001 | 2.330 (1.612–3.973) | <0.001 | 31 |
| Echogenic foci | | | | | | |
| None or large comet-tail artifacts | 81 (26.5%) | 140 (45.0%) | | 1 | | |
| Macrocalcifications | 13 (4.2%) | 20 (6.4%) | | 0.936 (0.378–2.315) | 0.886 | |
| Peripheral calcifications | 6 (2.0%) | 3 (1.0%) | | 0.938 (0.207–4.252) | 0.934 | |
| Punctate echogenic foci | 206 (67.3%) | 148 (47.6%) | <0.001 | 1.588 (1.051–2.400) | 0.082 | |
| No. of removed LNs in CC | | | | | | |
| ≥6 | 254 (83.0%) | 262 (84.2%) | | | | |
| <6 | 52 (17.0%) | 49 (15.8%) | 0.678 | | | |

*Y, year; SD, standard deviation; BMI, body mass index; CLT, chronic lymphocytic thyroiditis; ETE, extrathyroidal extension; CLNM, central lymph node metastasis; LN, lymph node; CC, central compartment.*

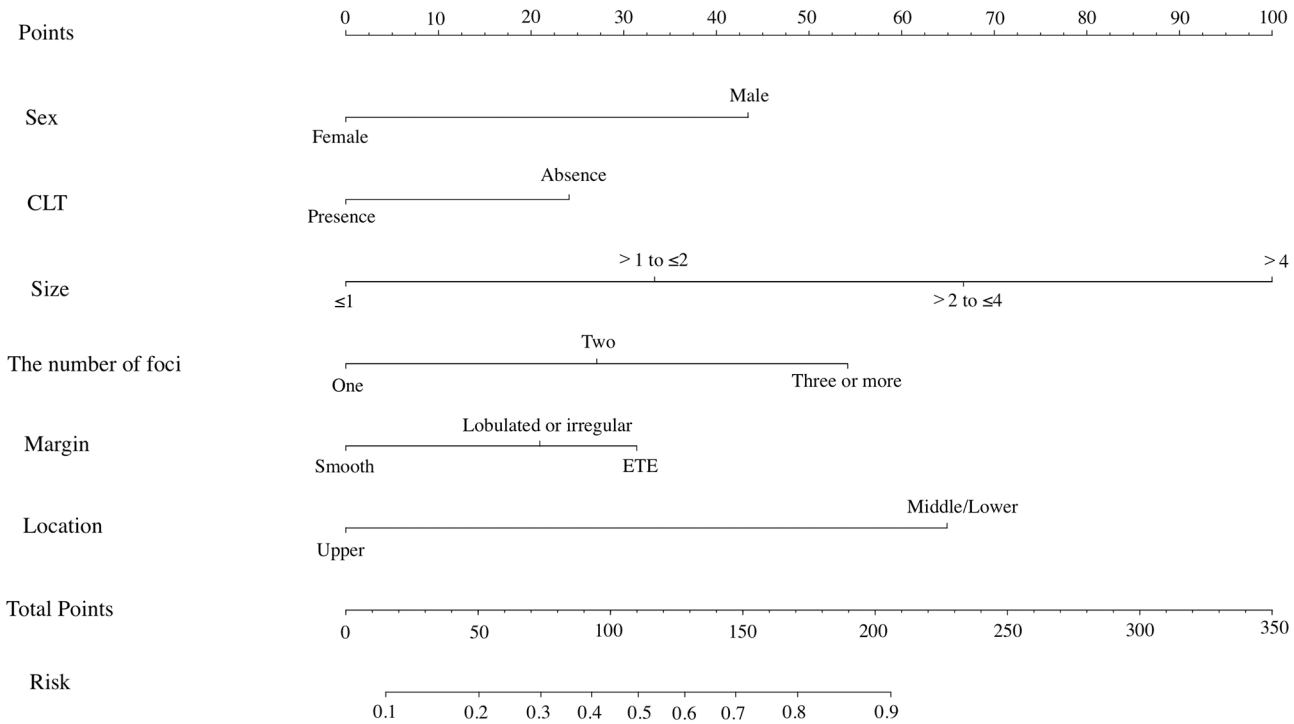


**FIGURE 2** | The nomogram for predicting CLNM in patients with PTC.

Decisions regarding the extent of surgery for the patient with PTC are mainly based on the preoperative assessment of lymph node status. But the role of prophylactic CND for clinically lymph node-negative (cN0) patients with PTC is still under debate. Supporters pointed that prophylactic CND not only eliminated potential recurrent sources, thereby reducing the risk of reoperation, but also improved the accuracy of staging (12, 13). Considering the potential complications of prophylactic CND, such as permanent hypoparathyroidism, recurrent laryngeal nerve injury and so on, opponents hold the view that prophylactic CND had the low prognostic benefits and many surgeons worldwide still preferred therapeutic CND only (14, 15). For cN0 PTC patients, the incidence of CLNM detected by histopathological examination ranged from 31% to 60.9% according to previous reports (16, 17). Therefore, routine CND is preferred for patients with PTC in our country due to the high risk of CLNM and unreliability of preoperative examinations in detecting CLNM.

The incidence of CLNM in our study was 49.3%, which was in accordance with the data of 24% to 58% reported in other studies (18, 19). We aimed to develop a nomogram, which could behave as a novel strategy to personalize and quantify the probability of CLNM in patients with PTC. Although some previous studies have also attempted to develop nomograms to predict CLNM for PTC patients, there were some limitations. For example, despite a nomogram with good discrimination (AUC=0.764) was built by Thompson et al. (13), only four variables were considered in this nomogram, which limited the clinical guidance. Moreover, these results were not reproducible in the external validation (AUC=0.615). Based on the 845 cN0 PTC patients with tumor size larger than 2 cm, Lang et al. (20) developed a nomogram, which showed a low discrimination (AUC=0.69) and was not validated in this study. Although enrolled larger patient cohorts, the AUC of 0.711 was not high for the nomogram established by Wang et al (21). In our study, we not only evaluated a large number of PTC patients, but also conducted both internal and external verification.

According to our findings, sex, CLT, tumor size, the number of foci, tumor location, margin were independent risk factors of CLNM among PTC patients by both univariate and multivariate analysis. Many clinicopathological factors related to CLNM have been reported previously, including sex (22–24), tumor size (13, 25), location (26), ETE (27), and the number of foci (28, 29). The incidence of PTC in women was significantly higher than that in men, and the ratio of women to men was approximately 3.7:1. However, the rate of CLNM in men was significantly higher than that in women (22–24). The relationship between multifocality and CLNM remains controversial (30). We divided the multifocality into unilateral multifocality and bilateral multifocality according to the location of tumors, and we found multifocality was not the independent risk factor of CLNM by multivariate logistic regression analysis. Instead of limited to investigating the difference between solitary and multifocal tumors, we further investigated the significance of the number of tumor foci on the incidence of CLNM. We found the proportion of CLNM increased with the number of foci, which was consistent with the study of Afif et al. (28) and Qu et al. (29).

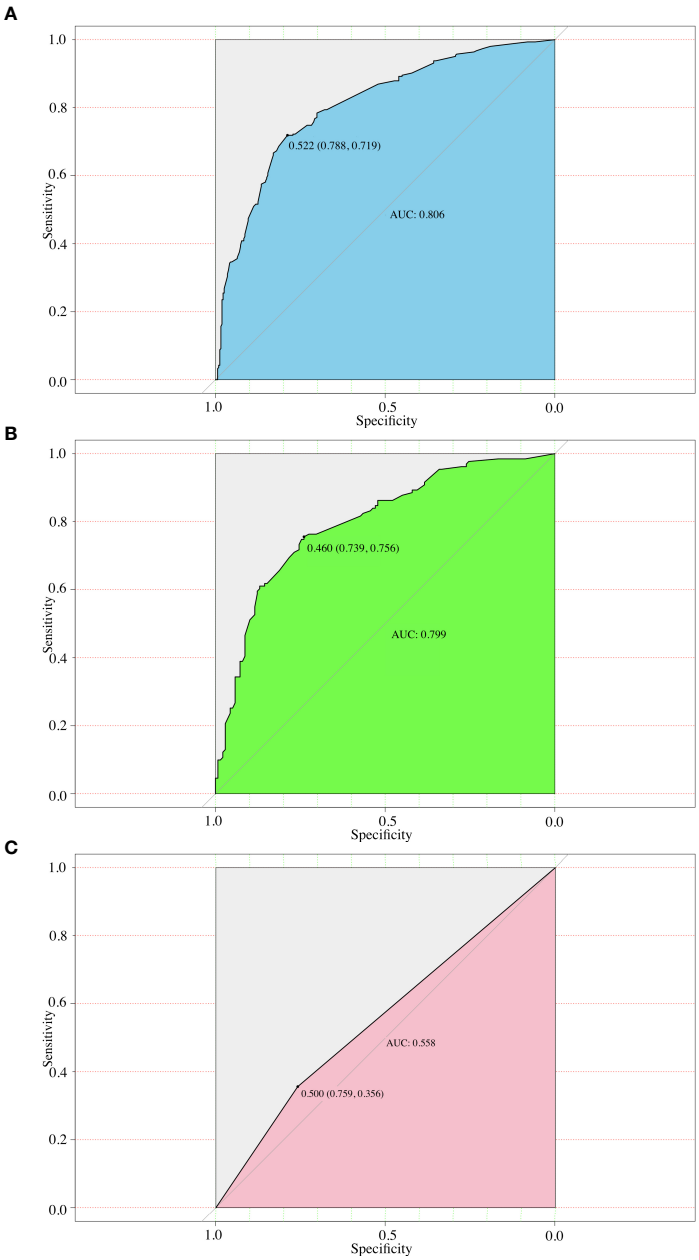


**FIGURE 3** | ROC curves for different models. **(A)** The ROC of the training group (AUC =0.806); **(B)** The ROC of the validation group (AUC =0.799); **(C)** The ROC of the preoperative US (AUC=0.558).

PTC cells from the upper region are more likely to be transported to the lateral lymph nodes through the lymph flow along the superior thyroid artery (31). Hence, tumor located in the upper pole of the thyroid lobe conferred a lower risk of CLNM and a higher risk of lateral cervical metastasis. It was known that larger tumor size was associated with more aggressive features in PTC. Interestingly, tumor size was the largest contributor to scores in our nomogram. Considering the guiding role of the nomogram before surgery, we took ETE diagnosed by preoperative US as variable instead of pathological ETE in this study. As reported, US showed high sensitivity (80%) for predicting minimal ETE of PTC (32). In addition, when US and magnetic resonance imaging (MRI) are combined, the diagnostic value of preoperative prediction of ETE would be greatly improved. Since our study is a retrospective study, MRI examinations were not performed for all patients. But we found lobulated or irregular margin and ETE detected by US were independent risk factors of CLNM. The pathogenetic mechanisms linking CLT and PTC are still poorly understood since1955 when the association between CLT and PTC was first proposed. Some mechanisms, such as elevated

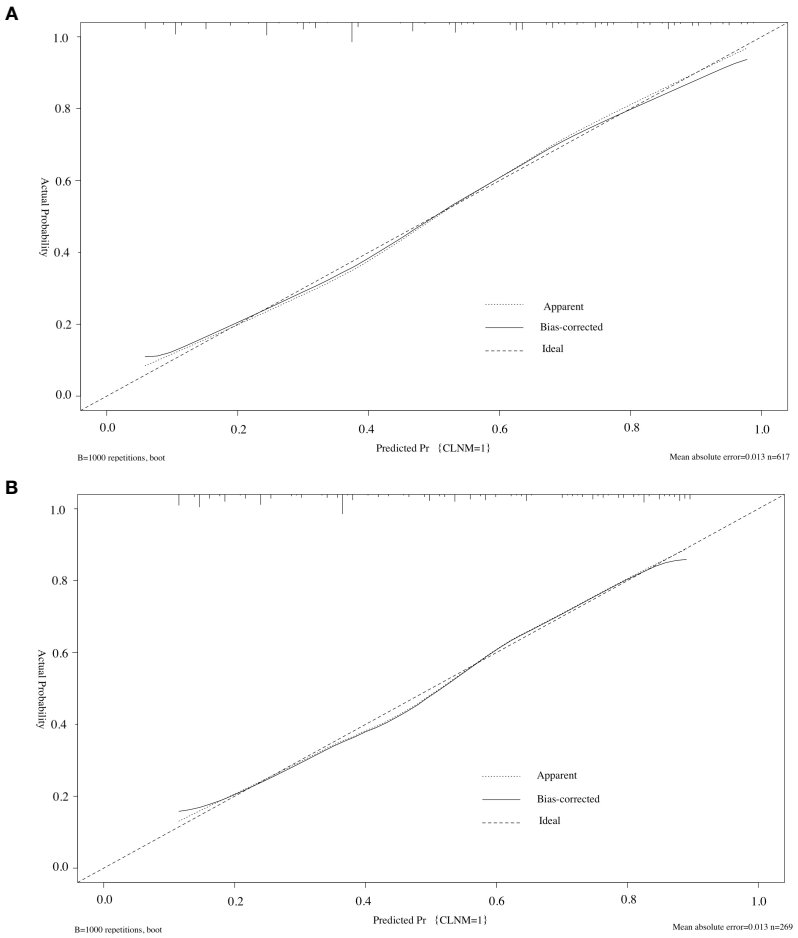


**FIGURE 4** | Calibration curve of the model in the training cohorts **(A)** and validation cohorts **(B)**. The diagonal dashed line represents the ideal prediction by the perfect nomogram; the solid line represents the calibration estimate from internally validated model; the dotted line indicates the apparent predictive accuracy. The closer the solid line is to the dotted line, the stronger the predictive ability of the model.

**TABLE 3** | Metastasis risk stratification of patients with PTC based on risk scores of nomogram model.

| Nomogram | ELR | LR | MR | HR | Total | Total *P* value | ELR-LR | ELR-MR | ELR-HR | LR-MR | LR-HR | MR-HR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0-50 | 51-100 | 101-150 | >150 | | | *P* value | *P* value | *P* value | *P* value | *P* value | *P* value |
| Training dataset | | | | | | | | | | | | |
| Without CLNM | 90 (87.4%) | 128 (70.3%) | 66 (37.9%) | 27 (17.1%) | 311 | | | | | | | |
| With CLNM | 13 (12.6%) | 54 (29.7%) | 108 (62.1%) | 131 (82.9%) | 306 | <0.001 | 0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Total | 103 | 182 | 174 | 158 | 617 | | | | | | | |
| Validation dataset | | | | | | | | | | | | |
| Without CLNM | 44 (88.0%) | 54 (68.4%) | 29 (39.7%) | 11 (16.4%) | 138 | | | | | | | |
| With CLNM | 6 (12.0%) | 25 (31.6%) | 44 (60.3%) | 56 (83.6%) | 131 | <0.001 | 0.011 | <0.001 | <0.001 | <0.001 | <0.001 | 0.002 |
| Total | 50 | 79 | 73 | 67 | 269 | | | | | | | |

*PTC, papillary thyroid carcinoma; CLNM, central lymph node metastasis; ELR, extreme low risk; LR, low risk; MR, moderated risk; HR, high risk.*

thyroid-stimulating hormone, RET/PTC rearrangement, and promoting tumor inflammation, have been proposed to explain the association between CLT and PTC (33). Our results showed that CLT was a protective factor against CLNM in PTC patients, which was in agreement with the meta-analysis of Lee et al. (34), that the lymphocytic infiltration counteracted tumor progression. Because the punctate echogenic foci were the strongest predictor of PTC in the US characteristics, the potential impact of microcalcification on CLNM should be discussed. In our study, echogenic foci were associated with the CLNM in the univariate analysis. But echogenic foci, especially punctate echogenic foci, were not the independent risk factors of CLNM by multivariate analysis. This may be due to other pathological structures, such as focal fibrosis of nodular goitres, which look similar to microcalcifications on US.

We incorporated the US characteristics and clinical risk factors into this easy-to-use nomogram, which may help individualized prediction of CLNM before surgery. The usage of nomogram is as follows: locate the patient's sex on the sex axis. Draw a line straight upward to the point axis to establish how many points toward the probability of CLNM the patient may get. Repeat the process for each of the other variables. Calculate total points for each of the predictors. Pinpoint the final score on the total point axis. Draw a line straight down to determine the patient's predicted probability of CLNM. For example, nomogram predicted a PTC male (43 points) patient with only one tumor (0 point) located in the middle portion (65 points), without CLT (24 points). According to US, the tumor had irregular margin (21 points), the size of tumor was 1.5cm (33 points). The total point was 186 for this patient. This patient had more than 80.0% chance of CLNM. By comparison with preoperative US, this nomogram showed a significant advantage over preoperative US (**Figure 3**). Apart from identifying the existence of CLNM, nomogram could also be used to guide surgeons to stratify patients so as to avoid unnecessary surgery. Based on the predictive nomogram, we proposed a risk stratification scheme and divided PTC patients into four quantified risk stratification (**Table 3**). For patients with different ratings, we can offer different treatment options. For example, for patients with extreme low risk or low risk of CLNM, prophylactic CND should be avoided to reduce surgical complications and damage; for patients with moderated risk of CLNM, prophylactic CND can be considered; for patients with high risk of CLNM, prophylactic CND is highly recommended to reduce the incidence of recurrence. In addition, for PTC patients who have not undergone CND, our nomogram may be helpful in detecting residual CLNM.

Despite some encouraging results were achieved, this study still had some limitations, which we would address in future studies. First, our study is a retrospective study. Compared with prospective studies, retrospective studies tend to have more errors and biases. For example, the criteria used to evaluate the US signature were subjective. Sonographers with insufficient experience may cause errors in a small sample. Nevertheless, the consensus of each feature among the sonographers in our study was consistent. The data we provided were extracted from the document and were not captured in the actual conversation. This model could also be improved by adding more useful technological parameters such as elastography and computer-aided diagnosis system. Second, the validation of the nomogram might be biased by institutional diagnostic patterns. Hence, strict external verification is required in prospective multi-center institutional trials to obtain more objective conclusions. Moreover, different surgeons were involved in performing thyroidectomy and lymph node dissection. Postoperative results, such as the number of metastasized lymph nodes may be affected by surgeon-specific factors.

In conclusion, our study found that CLNM was independently associated with sex, CLT, tumor size, the number of foci, tumor location, and margin. By using above variables, we constructed a nomogram that stratifies PTC patients into four groups that possess different CLNM risk levels. Clinicians can use these nomograms to evaluate the status of lymph nodes in PTC patients and consider prophylactic CND and meticulous postoperative evaluation for those with high scores.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

This study has been approved by the Institutional Review Board of Changzhou First People's Hospital ethics committee, and has been performed according to the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

## AUTHOR CONTRIBUTIONS

J-WF and L-ZH: writing - original draft, software, and data curation. S-YL: validation, formal analysis, and data curation. W-XW: conceptualization. FW and JH: validation and investigation. JY and YJ: writing - review & editing, visualization, and supervision. All authors contributed to the article and approved the submitted version.

## FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## ACKNOWLEDGMENTS

Lei Qin, the English language editor, was responsible for correcting language and grammar issues.

## REFERENCES

1. Roman BR, Morris LG, Davies L. The thyroid cancer epidemic, 2017 perspective. *Curr Opin Endocrinol Diabetes Obes* (2017) 24(5):332–6. doi: 10.1097/MED.0000000000000359
2. Yu XM, Wan Y, Sippel RS, Chen H. Should all papillary thyroid microcarcinomas be aggressively treated? An analysis of 18,445 cases. *Ann Surg* (2011) 254(4):653–60. doi: 10.1097/SLA.0b013e318230036d
3. Chow SM, Law SC, Chan JK, Au SK, Yau S, Lau WH. Papillary microcarcinoma of the thyroid-Prognostic significance of lymph node metastasis and multifocality. *Cancer* (2003) 98(1):31–40. doi: 10.1002/cncr.11442
4. Mehanna H, Al-Maqbili T, Carter B, Martin E, Campain N, Watkinson J, et al. Differences in the recurrence and mortality outcomes rates of incidental and nonincidental papillary thyroid microcarcinoma: a systematic review and meta-analysis of 21 329 person-years of follow-up. *J Clin Endocrinol Metab* (2014) 99(8):2834–43. doi: 10.1210/jc.2013-2118

5. Jiang LH, Yin KX, Wen QL, Chen C, Ge MH, Tan Z. Predictive Risk-scoring Model For Central Lymph Node Metastasis and Predictors of Recurrence in Papillary Thyroid Carcinoma. *Sci Rep* (2020) 10(1):710. doi: 10.1038/s41598-019-55991-1
6. Lee J, Song Y, Soh EY. Central lymph node metastasis is an important prognostic factor in patients with papillary thyroid microcarcinoma. *J Korean Med Sci* (2014) 29(1):48–52. doi: 10.3346/jkms.2014.29.1.48
7. Kim E, Park JS, Son KR, Kim JH, Jeon SJ, Na DG. Preoperative diagnosis of cervical metastatic lymph nodes in papillary thyroid carcinoma: comparison of ultrasound, computed tomography, and combined ultrasound with computed tomography. *Thyroid* (2008) 18(4):411. doi: 10.1089/thy.2007.0269
8. Guidoccio F, Grosso M, Orsini F, Boni G, Mariani G, Volterrani D. Thyroid Ultrasound and Other Imaging Procedures in the Pediatric Age. *Curr Pediatr Rev* (2016) 12(4):253–64. doi: 10.2174/1573396312666161031162436
9. 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* (2016) 26(1):1–133. doi: 10.1089/thy.2015.0020
10. Carty SE, Cooper DS, Doherty GM, Duh QY, Kloos RT, Mandel SJ, et al. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. *Thyroid* (2009) 19(11):1153–8. doi: 10.1089/thy.2009.0159
11. Grani G, Carbotta G, Nesca A, D'Alessandri M, Vitale M, Del Sordo M, et al. A comprehensive score to diagnose Hashimoto's thyroiditis: a proposal. *Endocrine* (2015) 49(2):361–5. doi: 10.1007/s12020-014-0441-5
12. Moo TA, McGill J, Allendorf J, Lee J, Fahey T 3rd, Zarnegar R. Impact of prophylactic central neck lymph node dissection on early recurrence in papillary thyroid carcinoma. *World J Surg* (2010) 34(6):1187–91. doi: 10.1007/s00268-010-0418-3
13. Thompson AM, Turner RM, Hayen A, Aniss A, Jalaty S, Learoyd DL, et al. A preoperative nomogram for the prediction of ipsilateral central compartment lymph node metastases in papillary thyroid cancer. *Thyroid* (2014) 24(4):675–82. doi: 10.1089/thy.2013.0224
14. Chen L, Wu YH, Lee CH, Chen HA, Loh EW, Tam KW. Prophylactic Central Neck Dissection for Papillary Thyroid Carcinoma with Clinically Uninvolved Central Neck Lymph Nodes: A Systematic Review and Meta-analysis. *World J Surg* (2018) 42(9):2846–57. doi: 10.1007/s00268-018-4547-4
15. Sancho JJ, Lennard TW, Paunovic I, Triponez F, Sitges-Serra A. Prophylactic central neck disection in papillary thyroid cancer: a consensus report of the European Society of Endocrine Surgeons (ESES). *Langenbecks Arch Surg* (2014) 399(2):155–63. doi: 10.1007/s00423-013-1152-8
16. Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. *Ann Surg* (2003) 237(3):399–407. doi: 10.1097/01.SLA.0000055273.58908.19
17. Lim YC, Choi EC, Yoon YH, Kim EH, Koo BS. Central lymph node metastases in unilateral papillary thyroid microcarcinoma. *Br J Surg* (2009) 96(3):253–7. doi: 10.1002/bjs.6484
18. Usluogullari CA, Onal ED, Ozdemir E, Ucler R, Kiyak G, Ersoy PE, et al. A retrospective analysis of prognostic factors predictive of lymph-node metastasis and recurrence in thyroid papillary microcarcinoma. *Minerva Endocrinol* (2015) 40(1):15–22.
19. Lee KE, Chung IY, Kang E, Koo do H, Kim KH, Kim SW, et al. Ipsilateral and contralateral central lymph node metastasis in papillary thyroid cancer: patterns and predictive factors of nodal metastasis. *Head Neck* (2013) 35(5):672–6. doi: 10.1002/hed.23016
20. Lang BH, Chai YJ, Cowling BJ, Min HS, Lee KE, Youn YK. Is BRAFV600E mutation a marker for central nodal metastasis in small papillary thyroid carcinoma? *Endocr Relat Cancer* (2014) 21(2):285–95. doi: 10.1530/ERC-13-0291
21. Wang Y, Guan Q, Xiang J. Nomogram for predicting central lymph node metastasis in papillary thyroid microcarcinoma: A retrospective cohort study of 8668 patients. *Int J Surg* (2018) 55:98–102. doi: 10.1016/j.ijsu.2018.05.023
22. Ardito G, Revelli L, Giustozzi E, Salvatori M, Fadda G, Ardito F, et al. Aggressive papillary thyroid microcarcinoma: prognostic factors and therapeutic strategy. *Clin Nucl Med* (2013) 38(1):25–8. doi: 10.1097/RLU.0b013e318279bc65
23. Jeon MJ, Chung MS, Kwon H, Kim M, Park S, Baek JH, et al. Features of papillary thyroid microcarcinoma associated with lateral cervical lymph node metastasis. *Clin Endocrinol (Oxf)* (2017) 86(6):845–51. doi: 10.1111/cen.13322
24. Liu LS, Liang J, Li JH, Liu X, Jiang L, Long JX, et al. The incidence and risk factors for central lymph node metastasis in cN0 papillary thyroid microcarcinoma: a meta-analysis. *Eur Arch Otorhinolaryngol* (2017) 274(3):1327–38. doi: 10.1007/s00405-016-4302-0
25. Kim SK, Woo JW, Lee JH, Park I, Choe JH, Kim JH, et al. Role of BRAF V600E mutation as an indicator of the extent of thyroidectomy and lymph node dissection in conventional papillary thyroid carcinoma. *Surgery* (2015) 158(6):1500–11. doi: 10.1016/j.surg.2015.05.016
26. Zhang L, Wei WJ, Ji QH, Zhu YX, Wang ZY, Wang Y, et al. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. *J Clin Endocrinol Metab* (2012) 97(4):1250–7. doi: 10.1210/jc.2011-1546
27. Giuseppe M, Andrea F, Corrado P, Debora F, Luigi R, Simonetta P, et al. Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. *Thyroid* (2009) 19(7):707–16. doi: 10.1089/thy.2008.0270
28. Al Afif A, Williams BA, Rigby MH, Bullock MJ, Taylor SM, Trites J, et al. Multifocal Papillary Thyroid Cancer Increases the Risk of Central Lymph Node Metastasis. *Thyroid* (2015) 25(9):1008–12. doi: 10.1089/thy.2015.0130
29. Qu N, Zhang L, Ji QH, Zhu YX, Wang ZY, Shen Q, et al. Number of tumor foci predicts prognosis in papillary thyroid cancer. *BMC Cancer* (2014) 14:914. doi: 10.1186/1471-2407-14-914
30. Iacobone M, Jansson S, Barczynski M, Goretzki P. Multifocal papillary thyroid carcinoma–a consensus report of the European Society of Endocrine Surgeons (ESES). *Langenbecks Arch Surg* (2014) 399(2):141–54. doi: 10.1007/s00423-013-1145-7
31. Lee YS, Shin SC, Lim YS, Lee JC, Wang SG, Son SM, et al. Tumor location-dependent skip lateral cervical lymph node metastasis in papillary thyroid cancer. *Head Neck* (2014) 36(6):887–91. doi: 10.1002/hed.23391
32. Kim H, Kim JA, Son EJ, Youk JH, Chung TS, Park CS, et al. Preoperative prediction of the extrathyroidal extension of papillary thyroid carcinoma with ultrasonography versus MRI: a retrospective cohort study. *Int J Surg* (2014) 12(5):544–8. doi: 10.1016/j.ijsu.2014.03.003
33. Vita R, Ieni A, Tuccari G, Benvenga S. The increasing prevalence of chronic lymphocytic thyroiditis in papillary microcarcinoma. *Rev Endocr Metab Disord* (2018) 19(4):301–9. doi: 10.1007/s11154-018-9474-z
34. Lee JH, Kim Y, Choi JW, Kim YS. The association between papillary thyroid carcinoma and histologically proven Hashimoto's thyroiditis: a meta-analysis. *Eur J Endocrinol* (2013) 168(3):343–9. doi: 10.1530/EJE-12-0903


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 10 May 2021
doi: 10.3389/fendo.2021.677986

# Metastasis of cN0 Papillary Thyroid Carcinoma of the Isthmus to the Lymph Node Posterior to the Right Recurrent Laryngeal Nerve

*Wei Du, Qigen Fang*, Xu Zhang and Liyuan Dai*

*Department of Head Neck and Thyroid, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China*

OPEN ACCESS

***Edited by:***
*Christoph Reiners, University Hospital Würzburg, Germany*

***Reviewed by:***
*Pietro Giorgio Calo, University of Cagliari, Italy*
*Giovanni Docimo, University of Campania Luigi Vanvitelli, Italy*

****Correspondence:***
*Qigen Fang*
*qigenfang@126.com*

***Specialty section:***
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

***Received:*** *08 March 2021*
***Accepted:*** *19 April 2021*
***Published:*** *10 May 2021*

***Citation:***
*Du W, Fang Q, Zhang X and Dai L (2021) Metastasis of cN0 Papillary Thyroid Carcinoma of the Isthmus to the Lymph Node Posterior to the Right Recurrent Laryngeal Nerve. Front. Endocrinol. 12:677986. doi: 10.3389/fendo.2021.677986*

**Objective:** The association between metastasis to the lymph node posterior to the right recurrent laryngeal nerve (LN-prRLN) and cN0 papillary thyroid carcinoma (PTC) located in the thyroid isthmus remains unknown; therefore, our goal was to analyze the characteristics of LN-prRLN metastasis of cN0 PTCs of the thyroid isthmus and determine its potential predictors.

**Patients and methods:** This retrospective study included patients who underwent bilateral central neck dissection between January 2018 and January 2021. The specimen was divided into five groups of prelaryngeal lymph node (LN), pretracheal LN, left paratracheal LN, lymph node anterior to the right recurrent laryngeal nerve (LN-arRLN), and LN-prRLN. Univariate and multivariate analyses were used to assess the association between the clinical pathologic variables and LN-prRLN metastases. Surgical complications were presented descriptively.

**Results:** A total of 357 patients were included, LN-prRLN metastasis occurred in 23 (6.4%) patients, and LN-prRLN was positive only when there were other LN metastases, especially LN-arRLN metastases. Other independent risk factors for LN-prRLN included foci numbers ≥2, tumor size ≥5.0 mm, and extrathyroidal extensions. The rates of permanent hypoparathyroidism and vocal cord paralysis were 1.1% and 2.0%, respectively.

**Conclusion:** LN-prRLN metastases should not be ignored in cN0 PTC located in the thyroid isthmus; however, its dissection is a safe procedure, and the status of LN-arRLN can be a reliable predictor for LN-prRLN metastases.

**Keywords: papillary thyroid carcinoma, thyroid isthmus, lymph node posterior to the right recurrent laryngeal nerve, central lymph node metastasis, lymph node anterior to the right recurrent laryngeal nerve**

# INTRODUCTION

Of all thyroid cancers, papillary thyroid carcinoma (PTC) is the most common histologic type. It has a relatively high occult central neck lymph node (LN) metastasis rate ranging from 25.7% to 60% (1–7). The importance of prophylactic central neck dissections (CNDs) in PTCs has been confirmed by a recent ATA guideline (8). Central neck LNs consist of prelaryngeal (Delphian) LNs, pretracheal LNs, and paratracheal LNs. Based on anatomical differences, the right paratracheal LNs are divided into two subgroups: LN posterior to the right recurrent laryngeal nerve (LN-prRLN) and LN anterior to the right recurrent laryngeal nerve (LN-arRLN). Dissection of the LN-prRLN requires patience and experience and could lead to nerve damage, affecting the patient's quality of life. Its use has been controversial and often overlooked.

However, there is increasing evidence that LN-prRLN metastases can occur in up to 26.6% of cN0 PTCs and that an additional removal procedure is not associated with an increased possibility of transient or permanent hypoparathyroidism or vocal cord paralysis (9–15). Common risk factors for LN-prRLN metastases include multiple foci, extrathyroidal extensions (ETE), right lobe tumors, tumor size, LN-arRLN metastases, and the number of positive LNs in the central neck. However, these finding were based on studies that included only patients with PTCs located in the right lobe (9) or with PTC, irrespective of tumor site (7, 10–12). Studies on patients with PTCs located in the isthmus had very limited sample sizes (13–15). However, PTCs located in the thyroid isthmus have significantly different pathologic features. They present with a higher incidence of multifocality, invasions of the thyroid capsules and adjacent tissues, and central node involvement compared to carcinomas located in other parts of the thyroid (16). Therefore, in current study, we aimed to analyze the metastatic characteristics of the LN-prRLN and its potential predictors in PTC located in the thyroid isthmus.

# PATIENTS AND METHODS

## Ethical Considerations

Our hospital Institutional Research Committee approved this study, and all the participants signed an informed consent agreement. All the procedures involving human participants were conducted in accordance with the ethical standards of the Institutional and/or National Research Committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Patient Selection

Medical records of all the patients (>18 years) who received surgical treatment for PTC between January 2018 and January 2021 were reviewed retrospectively. The selection criteria were as follows: having a primary PTC confirmed by postoperative pathology; location of the PTC in the thyroid isthmus without any suspicious malignant nodules in the bilateral thyroid lobes, confirmed with preoperative ultrasonography; presence of cN0 neck, confirmed with preoperative ultrasonography and computed tomography (CT). Patients with previous neck surgeries, family histories of cancer, and histories of neck radiotherapy were excluded. The following data were extracted and analyzed for the included patients: demographic data; pathologies including ETE, capsular invasions, perineural invasions (PNIs), and lymphovascular invasions (LVIs); BRAF 600E mutations; and postoperative complications.

## Definitions of Important Variables

An isthmus PTC was defined as a tumor with its boundaries within the lateral borders of the trachea (17). A cN0 neck was defined as a neck which did not have following features on ultrasonography: the absence of an echogenic hilum, a round shape, microcalcification, peripheral blood flow on color Doppler images, and cystic changes (18) and on CT: areas with clear evidence of nonfat, low-density, or liquid components; the largest diameter >15 mm at level II and >10 mm at other levels; and ratios of the longest to smallest diameter ≤2 (19). Tumor size was defined as the longest diameter of the tumor.

Capsular invasion was defined as the invasion of the thyroid capsular by a tumor and ETE as tumor invasion of structures outside the thyroid, including the trachea, anterior cervical muscle, larynx, and cricothyroid muscle. Both capsular invasion and ETE were evaluated based on intraoperative findings and postoperative pathologies.

## Surgical Treatment Procedures

There was no specific guideline for treating a cN0 PTC located in the thyroid isthmus in China. In our cancer center, there are two procedures available, total thyroidectomy and wide field isthmusectomy. The choice of treatment method depended on the surgeon's preference and the patient's condition.

From January 2018, a prophylactic bilateral CND was performed for all patients with cN0 PTCs located in the thyroid isthmus. The surgical specimens of patients were divided into five subgroups: prelaryngeal LN, pretracheal LN, left paratracheal LN, LN-arRLN, and LN-prRLN. A pathologic analysis was conducted separately for every patient.

## Statistical Analysis

The association between the clinical pathologic variables and LN-prRLN metastases was assessed first using a Chi-square test, and then to find the independent predictors, a multivariate analysis of the variables that were found to be significant in the univariate analysis was performed. All the statistical analyses were performed using SPSS 20.0, and a $P<0.05$ was considered to be significant.

# RESULTS

## Baseline Data of the Enrolled Patients

A total of 357 patients were included in the study; of these patients, 281 (78.7%) were female and 76 (21.3%) male. The

mean age was 47.6 years with a range of 20 to 68 years. The mean tumor size was 7.7 mm with a range from 1.7 to 13.6 mm. Coexistent Hashimoto's disease was found in 103 (28.9%) patients and BRAF 600E mutations were noted in 257 (72.0%) patients. Multiple foci (≥2) occurred in 31 (8.7%) patients, while ETE and capsular invasions were noted in 48 (13.4%) and 78 (21.8%) patients, respectively. PNI and LVI were observed in 26 (7.3%) and 21 (5.9%) patients, respectively. Total thyroidectomy and wide field isthmusectomy were performed in 204 (57.1%) and 153 (42.9%) patients, respectively.

## Central LN Metastatic Characteristics

Central LN metastases were noted in 129 (36.1%) patients. Prelaryngeal and pretracheal LN metastases occurred in 60 (16.8%) and 56 (15.7%) patients, respectively. Forty six (12.9%) patients had left paratracheal LN metastases, while LN-arRLN and LN-prRLN metastases occurred in 52 (14.6%) and 23 (6.4%) patients, respectively.

**Table 1** describes the metastatic pattern in the 129 patients. Prelaryngeal LN metastasis alone was the most common pattern, which occurred in 38.8% of the cases, followed by a pattern of concurrent metastases of the pretracheal LN, left paratracheal LN, and LN-arRLN. The two least common patterns were the metastases of the LN-arRLN and LN-prRLN and the metastases of the pretracheal LN and left paratracheal LN. There was no case of LN-prRLN metastasis alone.

## Predictor for LN-prRLN Metastases

The results of the univariate analysis (**Table 2**) showed that male patients had a LN-prRLN metastasis rate of 11.8%, which was significantly higher than the 5.0% observed in female patients ($P = 0.038$). In the 31 patients with multiple foci, 19.4% had LN-prRLN metastases, which was statistically different from the rate observed in 326 patients with solitary foci ($P = 0.009$). Fourteen (9.9%) of the 141 patients with tumor size ≥ 5.0 mm and 4.2% of the 216 patients with tumor size <5.0 mm had LN-prRLN metastases. The difference was significant ($P = 0.030$). A positive LN-prRLN was observed in 18.8% of patients with ETE. The rate was significantly higher than the 4.5% seen in patients without ETE ($P$=0.001). Of the patients with LN-arRLN metastases, 44.2% also had LN-prRLN metastases, and none of the patients without LN-arRLN metastases showed LN-prRLN metastases. The difference was significant ($P$<0.001).

**TABLE 1** | Pattern of the central lymph node (LN) metastasis in the 129 patients.

| Metastatic pattern | Number of patients (%) |
|---|---|
| Prelaryngeal LN | 50 (38.8%) |
| Pretracheal LN, left Paratracheal LN, LN-arRLN* | 24 (18.6%) |
| Left Paratracheal LN, LN-arRLN, LN-prRLN# | 21 (16.3%) |
| Pretracheal LN | 16 (12.4%) |
| Prelaryngeal LN, Pretracheal LN | 10 (7.8%) |
| Pretracheal LN, LN-arRLN | 5 (3.9%) |
| LN-arRLN, LN-prRLN | 2 (1.6%) |
| Pretracheal LN, left Paratracheal LN | 1 (0.8%) |

*There were no overlapping numbers among each pattern.*
**LN-arRLN, lymph node anterior to the right recurrent laryngeal nerve;*
*#LN-prRLN, lymph node posterior to the right recurrent laryngeal nerve.*

**TABLE 2** | Univariate analysis of predictor for lymph node posterior to the right recurrent nerve metastasis (LN-prRLN).

| Variables | LN-prRLN metastasis | | p |
|---|---|---|---|
| | Positive (n = 23) | Negative (n = 334) | |
| Age | | | |
| <55 | 10 (5.3%) | 180 (94.7%) | |
| ≥55 | 13 (7.8%) | 154 (92.2%) | 0.333 |
| Sex | | | |
| Female | 14 (5.0%) | 267 (95.0%) | |
| Male | 9 (11.8%) | 67 (88.2%) | 0.038 |
| Foci number | | | |
| 1 | 17 (5.2%) | 309 (94.8%) | |
| ≥2 | 6 (19.4%) | 25 (80.6%) | 0.009 |
| Hashimoto's disease | | | |
| No | 15 (5.9%) | 239 (94.1%) | |
| Yes | 8 (7.8%) | 95 (92.2%) | 0.516 |
| Tumor size | | | |
| <5.0 mm | 9 (4.2%) | 207 (95.8%) | |
| ≥5.0 mm | 14 (9.9%) | 127 (90.1%) | 0.030 |
| BRAF 600E mutation | | | |
| No | 6 (6.0%) | 94 (94.0%) | |
| Yes | 17 (6.6%) | 240 (93.4%) | 0.832 |
| ETE* | | | |
| No | 14 (4.5%) | 295 (95.5%) | |
| Yes | 9 (18.8%) | 39 (81.2%) | 0.001 |
| Capsular invasion | | | |
| No | 19 (6.8%) | 260 (93.2%) | |
| Yes | 4 (5.1%) | 74 (94.9%) | 0.624 |
| PNI# | | | |
| No | 21 (6.3%) | 310 (93.7%) | |
| Yes | 2 (7.7%) | 24 (92.3%) | 1.000 |
| LVI! | | | |
| No | 21 (6.3%) | 315 (93.7%) | |
| Yes | 2 (9.5%) | 19 (90.5%) | 0.636 |
| Prelaryngeal LN& metastasis | | | |
| No | 23 (7.7%) | 274 (92.3%) | |
| Yes | 0 | 60 (100%) | 0.037 |
| Pretracheal LN metastasis | | | |
| No | 22 (7.3%) | 279 (92.7%) | |
| Yes | 1 (1.8%) | 55 (98.2%) | 0.148 |
| Left paratracheal LN metastasis | | | |
| No | 2 (0.6%) | 309 (99.4%) | |
| Yes | 21 (45.7%) | 25 (54.3%) | <0.001 |
| LN-arRLN^ metastasis | | | |
| No | 0 | 305 (100%) | |
| Yes | 23 (44.2%) | 29 (55.8%) | <0.001 |

**ETE, extrathyroidal extension; #PNI, perineural invasion; !LVI, lymphovascular invasion; &LN, lymph node; ^ LN-arRLN, lymph node anterior to the right recurrent laryngeal nerve.*

The multivariate analysis showed that foci number ≥2, tumor size ≥5.0 mm, ETE, and LN-arRLN metastases were associated with an increased possibility of LN-prRLN metastases (all $P$<0.05, **Table 3**).

## Postoperative Complication

Transient hypoparathyroidism occurred in 47 patients (13.2%), and 43 cases gradually returned to be normal within 6 months after surgery, while four patients had permanent hypoparathyroidism, which was equivalent to a rate of 1.1%.

Hoarseness occurred in 17 (4.8%) patients immediately after surgery. During follow-up, the voice of 10 patients recovered

**TABLE 3 |** Multivariate analysis predictor for lymph node posterior to the right recurrent nerve metastasis.

| Variables | p | OR [95% CI] |
|---|---|---|
| Sex | 0.134 | 3.674 [0.663–9.552] |
| Foci number | 0.021 | 2.185 [1.291–8.335] |
| Tumor size | 0.004 | 2.675 [1.472–9.423] |
| ETE* | <0.001 | 5.765 [1.892–16.448] |
| Prelaryngeal LN[&] metastasis | 0.455 | 0.689 [0.112–10.382] |
| left Paratracheal LN metastasis | 0.217 | 3.288 [0.785–11.332] |
| LN-arRLN^ metastasis | <0.001 | 6.876 [2.118–20.674] |

**ETE, extrathyroidal extension; [&]LN, lymph node; ^LN-arRLN, lymph node anterior to the right recurrent laryngeal nerve.*

without vocal cord immobility confirmed by a direct laryngoscope; four patients had a normal voice with vocal cord paralysis, while three patients showed consistent voice change with vocal cord immobility.

## DISCUSSION

To our best knowledge, this was the first study to analyze the features of LN-prRLN metastasis of cN0 PTCs located in the thyroid isthmus. A metastasis rate of 6.4% was observed, and there was no skip metastasis of LN-prRLN. The status of LN-arRLN can be used as a reliable predictor for LN-prRLN metastases, and the dissection of the LN-prRLN did not increase the possibility of recurrent laryngeal nerve and parathyroid gland damage occurring.

A study by Grodski et al. found that LN-prRLN resection may be recommended in routine CNDs (20); however, this procedure was related to an increased risk of nerve injury due to the traction and elevation that occurs during the LN removal. Therefore, a series of researchers explored the incidence of LN-prRLN metastases, and the safety and necessity of LN-prRLN dissections. Lee et al. (13) enrolled 123 PTC patients, including 86 cases staged as T2-T4, and reported that 14 patients showed metastases in the LN-prRLN with an overall rate of 11.4%. Furthermore, all these patients had LN-arRLN metastases while skip metastases were not found. In addition, the T2-T4 tumors had a metastasis rate of 13.9%, which was comparable to the 5.4% found in T1 tumors. In a study by Liu et al. (15), which had a comparable sample size to that of Lee et al.'s study, the LN-prRLN metastasis rate was 11.0% in 145 PTC patients; however, four patients were negative for LN-arRLN metastasis.

However, several studies have reported higher rates and different findings than those of ours. Luo et al. (12) performed a prospective study that included 595 PTC patients, of whom a total of 102 (17.1%) patients had LN-prRLN metastases, and of these patients, 52 showed concurrent LN-arRLN negativity. In a large-scale study by Pinyi et al. (1) comprising 405 patients, LN-prRLN positivity was observed in 108 patients at a rate of 26.7%. The authors also noted that 26 patients showed LN-prRLN metastases without LN-arRLN positivity. Another large sample size study by Li et al. (10) found that LN-prRLN metastases occurred in 124 (15.1%) PTC patients, and of the 434 patients without LN-arRLN metastases, 41 (9.4%) presented LN-prRLN positivity. In a study by Chang et al. (21), which had the largest cohort size till date, of the 5556 enrolled patients, 148 were positive for LN-prRLN metastases and six did not have LN-arRLN metastases. The findings of these studies suggested that over 10% of PTC patients could have had a residual LN-prRLN disease if the dissections were not performed; however, we discovered that all of the authors had considered cN0, cN1a, and cN1b patients together. Thus, in theory, cN1 patients had increased possibility of occurrence of LN-prRLN metastases as well as that of skip metastases, making it acceptable that our incidence of LN-prRLN metastasis was 6.4% and that there was no skip metastasis observed.

A few authors have also evaluated the LN-prRLN metastases in cN0 patients. Li et al.(7) and Ito et al. (9) found that 28 (8.3%) of 338 patients and 127 (14%) of 922 patients had LN-prRLN metastases, respectively. These rates were still a little higher than the rates of our study. Usually PTCs located in the thyroid isthmus have more aggressive biologic behavior than that of PTCs arising from other sites of the thyroid (16). This viewpoint was supported by the fact that our overall central LN metastasis rate was 36.1%, which was higher than the rates in the studies by Li et al. (7) and Ito et al. (9). Moreover, the two most common metastatic sites were prelaryngeal and pretracheal LNs in the current study, which was consistent with results of previous similar studies (22). Our lower LN-prRLN metastasis rate may be explained by the small tumor size and lower multiplicity.

The safety of LN-prRLN dissection is a point of concern. Wang et al. (11) divided 1487 patients into two groups: the 378 patients who underwent CND with LN-prRLN dissection were defined as group A and the 1109 patients who underwent CND without LN-prRLN dissection as group B. Although group A had a higher incidence of hypocalcemia (7.4% *vs.* 4.0%, $P$=0.012), the two groups had similar rates of persistent hypocalcemia, transient and permanent recurrent laryngeal nerve palsies, chyle leakages, hematomas, and wound infections. Pinyi et al. (1) reported that transient recurrent laryngeal nerve injuries and hypoparathyroidism occurred in 1.0% and 1.7% patients in their cohort, respectively, and there was no persistent dysfunction. Similar results were also reported by Lee et al. (13), Yu et al. (14), Chang et al. (21), and us. All of these finding suggested LN-prRLN dissection is safe if it is performed patiently and meticulously. However, we must keep in mind that the daily life of the patients might be significantly affected if there was permanent dysfunction (23), some improvements had been introduced. Calò et al. (24) had commented intraoperative neuromonitoring had a very high sensitivity and negative predictive value, but also good specificity and positive predictive value in predicting postoperative nerve function during thyroid surgery and could assist the surgeon in intraoperative decision making. Docimo et al. (25) introduced a good option of total thyroidectomy without prophylactic central neck dissection combined with routine oral calcium and vitamin D supplements in selected differentiated thyroid cancer patients to prevent postoperative hypocalcemia for increasing the likelihood of a safe and early discharge from the hospital.

Risk factors for LN-prRLN metastases have been analyzed frequently. Age < 45 years, male sex, tumor sizes>1 cm, lateral LN metastases, ETE, multifocalities, capsule invasions, LN-arRLN metastases, and central LN metastases were all reported to be associated with LN-prRLN metastases (22). Our findings also supported these conclusions. Moreover it was noted that LN-prRLN was positive only when there were other LNs metastases, especially LN-arRLN metastasis. This finding is highly significant as it indicates that an intraoperative pathologic examination of the LN-arRLN could determine which patients would require LN-prRLN dissection.

This study had some limitations. First, this was a retrospective study with an inherent selection bias. Second, our sample size was relatively small, and more studies are required to validate the findings. Third, without a control group or survival data, our statistical power was decreased.

In summary, while LN-prRLN metastases of cN0 PTC located in the thyroid isthmus is not common, it should not be ignored; its dissection was found to be a safe procedure. LN-arRLN metastases were the most significant risk factor for LN-prRLN metastases, and it could act as a reliable predictor for LN-prRLN metastases.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Henan Cancer Hospital ethics committee. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

All the authors made the contribution in study design, manuscript writing, studies selecting, data analysis, study quality evaluating, and manuscript revising. All authors contributed to the article and approved the submitted version.

## REFERENCES


1. Pinyi Z, Bin Z, Jianlong B, Yao L, Weifeng Z. Risk Factors and Clinical Indication of Metastasis to Lymph Nodes Posterior to Right Recurrent Laryngeal Nerve in Papillary Thyroid Carcinoma: A Single-Center Study in China. *Head Neck* (2014) 36:1335–42. doi: 10.1002/hed.23451
2. Mukherjee D, Arnav A, Agarwal K, Sharma R, Saidha N. Prophylactic Central Node Dissection in Differentiated Thyroid Cancer: A Prospective Tertiary Care Center Experience. *Cancer Treat Res Commun* (2020) 25:100228. doi: 10.1016/j.ctarc.2020.100228
3. Zhang L, Liu H, Xie Y, Xia Y, Zhang B, Shan G, et al. Risk Factors and Indication for Dissection of Right Paraesophageal Lymph Node Metastasis in Papillary Thyroid Carcinoma. *Eur J Surg Oncol* (2016) 42:81–6. doi: 10.1016/j.ejso.2015.10.011
4. Conzo G, Tartaglia E, Avenia N, Calò PG, de Bellis A, Esposito K, et al. Role of Prophylactic Central Compartment Lymph Node Dissection in Clinically N0 Differentiated Thyroid Cancer Patients: Analysis of Risk Factors and Review of Modern Trends. *World J Surg Oncol* (2016) 14:149. doi: 10.1186/s12957-016-0879-4
5. Calò PG, Lombardi CP, Podda F, Sessa L, Santini L, Conzo G. Role of Prophylactic Central Neck Dissection in Clinically Node-Negative Differentiated Thyroid Cancer: Assessment of the Risk of Regional Recurrence. *Updates Surg* (2017) 69:241–8. doi: 10.1007/s13304-017-0438-8
6. Medas F, Canu GL, Cappellacci F, Boi F, Lai ML, Erdas E, et al. Predictive Factors of Lymph Node Metastasis in Patients With Papillary Microcarcinoma of the Thyroid: Retrospective Analysis on 293 Cases. *Front Endocrinol (Lausanne)* (2020) 11:551. doi: 10.3389/fendo.2020.00551
7. Li F, Wu Y, Chen L, Hu L, Liu X. Evaluation of Clinical Risk Factors for Predicting Insidious Right Central and Posterior Right Recurrent Laryngeal Nerve Lymph Node Metastasis in Papillary Thyroid Microcarcinoma Patients (cN0): Experience of a Single Center. *Ann Transl Med* (2019) 7:8. doi: 10.21037/atm.2018.12.43
8. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 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* (2016) 26:1–133. doi: 10.1089/thy.2015.0020
9. Ito Y, Fukushima M, Higashiyama T, Kihara M, Takamura Y, Kobayashi K, et al. Incidence and Predictors of Right Paraesophageal Lymph Node Metastasis of N0 Papillary Thyroid Carcinoma Located in the Right Lobe. *Endocr J* (2013) 60:389–92. doi: 10.1507/endocrj.EJ12-0362
10. Li J, He G, Tong Y, Tao L, Xie L, Gao L, et al. A Novel Scoring System for the Risk of Papillary Thyroid Cancer Metastases in Lymph Nodes Posterior to the Right of the Recurrent Laryngeal Nerve. *Endocr Pract* (2021) 27:15–20. doi: 10.4158/EP-2020-0129
11. Wang Y, Wang D, Chen L, Guo K, Sun T. A Comparison of Two Operation Methods Revealed the Risk Factors and the Necessity of LN-prRLN Dissection in Papillary Thyroid Carcinoma: A Retrospective Cohort Study in FUSCC. *Int J Endocrinol* (2020) 2020:7162793. doi: 10.1155/2020/7162793
12. Luo Y, Xu XC, Shen J, Shi JJ, Lu S, He W, et al. Model of Lymph Node Metastasis Posterior to the Right Recurrent Laryngeal Nerve in Papillary Thyroid Carcinoma. *Cancer Manag Res* (2018) 10:2449–55. doi: 10.2147/CMAR.S167997
13. Lee BJ, Lee JC, Wang SG, Kim YK, Kim IJ, Son SM. Metastasis of Right Upper Para-Esophageal Lymph Nodes in Central Compartment Lymph Node Dissection of Papillary Thyroid Cancer. *World J Surg* (2009) 33:2094–8. doi: 10.1007/s00268-009-0149-5
14. Yu QA, Ma DK, Liu KP, Wang P, Xie CM, Wu YH, et al. Clinicopathologic Risk Factors for Right Paraesophageal Lymph Node Metastasis in Patients With Papillary Thyroid Carcinoma. *J Endocrinol Invest* (2018) 41:1333–8. doi: 10.1007/s40618-018-0874-4
15. Liu Z, Sun M, Xiao Y, Yang J, Zhang T, Zhao Y. Predictors of Metastasis to Lymph Nodes Posterior to the Right Recurrent Laryngeal Nerve in Differentiated Thyroid Carcinoma: A Prospective Study. *Asian J Surg* (2017) 40:270–7. doi: 10.1016/j.asjsur.2015.12.003
16. Vasileiadis I, Boutzios G, Karalaki M, Misiakos E, Karatzas T. Papillary Thyroid Carcinoma of the Isthmus: Total Thyroidectomy or Isthmusectomy? *Am J Surg* (2018) 216:135–9. doi: 10.1016/j.amjsurg.2017.09.008
17. Song CM, Lee DW, Ji YB, Jeong JH, Park JH, Tae K. Frequency and Pattern of Central Lymph Node Metastasis in Papillary Carcinoma of the Thyroid Isthmus. *Head Neck* (2016) 38 Suppl 1:E412–6. doi: 10.1002/hed.24009
18. Tang S, Buck A, Jones C, Sara Jiang X. The Utility of Thyroglobulin Washout Studies in Predicting Cervical Lymph Node Metastases: One Academic

Medical Center's Experience. *Diagn Cytopathol* (2016) 44:964–8. doi: 10.1002/dc.23554
19. Lee Y, Kim JH, Baek JH, Jung SL, Park SW, Kim J, et al. Value of CT Added to Ultrasonography for the Diagnosis of Lymph Node Metastasis in Patients With Thyroid Cancer. *Head Neck* (2018) 40:2137–48. doi: 10.1002/hed.25202
20. Grodski S, Cornford L, Sywak M, Sidhu S, Delbridge L. Routine Level VI Lymph Node Dissection for Papillary Thyroid Cancer: Surgical Technique. *ANZ J Surg* (2007) 77:203–8. doi: 10.1111/j.1445-2197.2007.04019.x
21. Chang H, Yoo RN, Kim SM, Kim BW, Lee YS, Lee SC, et al. The Clinical Significance of the Right Para-Oesophageal Lymph Nodes in Papillary Thyroid Cancer. *Yonsei Med J* (2015) 56:1632–7. doi: 10.3349/ymj.2015.56.6.1632
22. Li C, Xiang J, Wang Y. Risk Factors for Predicting Lymph Nodes Posterior to Right Recurrent Laryngeal Nerve (LN-Prrln) Metastasis in Thyroid Papillary Carcinoma: A Meta-Analysis. *Int J Endocrinol* (2019) 2019:7064328. doi: 10.1155/2019/7064328
23. Conzo G, Docimo G, Mauriello C, Gambardella C, Esposito D, Cavallo F, et al. The Current Status of Lymph Node Dissection in the Treatment of Papillary Thyroid Cancer. *A Literature Rev Clin Ter* (2013) 164:e343–6.
24. Calò PG, Medas F, Conzo G, Podda F, Canu GL, Gambardella C, et al. Intraoperative Neuromonitoring in Thyroid Surgery: Is the Two-Staged Thyroidectomy Justified? *Int J Surg* (2017) 41 Suppl 1:S13–20. doi: 10.1016/j.ijsu.2017.02.001
25. Docimo G, Tolone S, Ruggiero R, Gubitosi A, Pasquali D, De Bellis A, et al. Total Thyroidectomy Without Prophylactic Central Neck Dissection Combined With Routine Oral Calcium and Vitamin D Supplements: Is it a Good Option to Achieve a Low Recurrence Rate Avoiding Hypocalcemia? A retrospective study. *Minerva Chir* (2013) 68:321–8.

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 27 May 2021
doi: 10.3389/fendo.2021.646793

# Analysis of the Prognostic Value and Potential Molecular Mechanisms of TREM-1 Overexpression in Papillary Thyroid Cancer *via* Bioinformatics Methods

*Zhenyu Xie*[†], *Xin Li*[†], *Yuzhen He*, *Song Wu*, *Shiyue Wang*, *Jianjian Sun*, *Yuchen He*, *Yu Lun*, *Shijie Xin and Jian Zhang*[*]

*Department of Vascular and Thyroid Surgery, The First Hospital, China Medical University, Shenyang, China*

**Background:** Triggering receptor expressed on myeloid cells-1 (TREM-1) has been reported as a biomarker in many cancers. However, the biological function of TREM-1 in papillary thyroid carcinoma (PTC) remains unknown.

**Methods:** We obtained TREM-1 expression data from The Cancer Genome Atlas (TCGA) database. Enrichment analysis of coexpressed genes and *TREM-1* methylation analysis were performed *via* LinkedOmics. The correlations between TREM-1 and immune infiltrates were investigated *via* ESTIMATE, TIMER and TISIDB. We analyzed the association of TREM-1 expression with pan-cancer overall survival *via* Gene Expression Profiling Interactive Analysis (GEPIA).

**Results:** *TREM-1* has lower methylation levels and higher expression levels in PTC tissues compared to normal tissues. TREM-1 expression is significantly associated with poor prognosis, advanced T classification, advanced N classification, and an increased incidence of *BRCA2* and *BRAF* mutations. Genes coexpressed with *TREM-1* primarily participate in immune-related pathways. TREM-1 expression is positively correlated with immune infiltration, tumor progression and poor overall survival across cancers.

**Conclusions:** TREM-1 is a good prognostic and diagnostic biomarker in PTC. TREM-1 may promote thyroid cancer progression through immune-related pathways. Methylation may act as an upstream regulator of TREM-1 expression and biological function. Additionally, TREM-1 has broad prognostic value in a pan-cancer cohort.

**Keywords: TREM-1, papillary thyroid carcinoma, diagnostic biomarker, prognostic biomarker, immune infiltration, DNA methylation**

OPEN ACCESS

***Edited by:***
*Christoph Reiners, University Hospital Würzburg, Germany*

***Reviewed by:***
*Cornelia Braicu, Iuliu Haţieganu University of Medicine and Pharmacy, Romania*
*Fu Lei, Chinese Academy of Agricultural Sciences, China*

***Correspondence:**
*Jian Zhang*
*jianzhang@cmu.edu.cn*

[†]*These authors have contributed equally to this work and share first authorship*

***Specialty section:***
*This article was submitted to Cancer Endocrinology, a section of the journal Frontiers in Endocrinology*

***Received:*** *28 December 2020*
***Accepted:*** *03 May 2021*
***Published:*** *27 May 2021*

***Citation:***
*Xie Z, Li X, He Y, Wu S, Wang S, Sun J, He Y, Lun Y, Xin S and Zhang J (2021) Analysis of the Prognostic Value and Potential Molecular Mechanisms of TREM-1 Overexpression in Papillary Thyroid Cancer via Bioinformatics Methods. Front. Endocrinol. 12:646793. doi: 10.3389/fendo.2021.646793*

# INTRODUCTION

Thyroid carcinoma (1) is the most prevalent endocrine malignancy, and its global incidence has rapidly increased in recent decades (2). Papillary thyroid carcinoma (PTC) is the most common type of TC and accounts for nearly 85% of all thyroid cancers (3). With standardized treatment, PTC often exhibits a favorable prognosis, with a 10-year survival rate of 93% (4). However, a high tendency of early lymph node metastasis or recurrence occurs in more than 30% cases (5). Therefore, identifying reliable and accurate biomarkers for the diagnosis and prognosis of PTC is essential.

Triggering receptor expressed on myeloid cells-1 (TREM-1) is a cell surface receptor belonging to the immunoglobulin superfamily (6). The function of TREM-1 is to enhance the inflammatory response by inducing large amounts of proinflammatory mediators (6). Human TREM-1 is predominantly expressed by blood neutrophils and by a subset of monocytes/macrophages (7). Furthermore, TREM-1 is also highly expressed by neutrophils and epithelial cells in skin and lymph nodes infected with bacteria or fungi (8). The tissue distribution of TREM-1 expression indicates a role for TREM-1 in inflammation (9). Because TREM-1 is widely distributed throughout the body and plays an important role in the inflammatory process, it has attracted great attention in the context of tumor formation, development and metastasis. TREM-1 overexpression has been reported in many malignancies and correlates with poor prognosis. A previous study has indicated that lung cancer cells upregulate TREM-1 expression and that tumor-associated macrophages have increased levels of TREM-1 (10). Functional experiments involving hepatocellular carcinoma (HCC) have suggested that TREM-1 promotes proliferation, increases invasiveness and inhibits apoptosis of HCC cells (11, 12). TREM-1 is involved in the establishment of a prognossis model for liver cancer (13). High-risk prognostic subgroups defined by TREM-1 expression have been identified for colorectal cancer (CRC) (14). In addition, signaling *via* TREM-1 is significantly related to the development and progression of chronic lymphocytic leukemia (15). TREM-1 is induced in macrophages by the androgen receptor signaling pathway in prostate cancer, and increases the motility and invasive capacity of prostate cancer cells (16). In recent years, many studies have suggested various strategies for regulating TREM-1 expression and activity to block the interaction between TREM-1 and its ligands to treat a number of diseases, including cancer (17, 18).

However, the biological function of TREM-1 in PTC remains unknown. Here, we investigated TREM-1 expression in PTC patients using data from The Cancer Genome Atlas (TCGA) and the National Center for Biotechnology Information Gene Expression Omnibus (GEO) databases. Through multidimensional analysis, we evaluated the genomic functional networks related to TREM-1 in PTC and further explored the role of TREM-1 in tumor immunity. Our results suggested that TREM-1 may be a new potential target for PTC diagnosis and treatment.

# MATERIALS AND METHODS

## Materials

The TCGA THCA dataset, containing normal thyroid samples (N) =58 and PTC samples (T) =512, was selected as the discovery cohort. The normalized RNA-seq data (FPKM, level three), DNA methylation data and single nucleotide variation data (VarScan) were downloaded from TCGA *via* the Genomic Data Commons (GDC) portal (https://portal.gdc.cancer.gov/). The clinical data of the TCGA THCA dataset were downloaded from the University of California at Santa Cruz (UCSC) Xena browser (https://xena.ucsc.edu/).

To assess the diagnostic value of TREM-1, we selected datasets containing both PTC and normal tissues in the GEO database. The following six RNA-seq microarray datasets were downloaded from the National Center for Biotechnology Information GEO database (http://www.ncbi.nlm.nih.gov/geo): GSE3467 (N=9, T=9), GSE27155 (N=4, T=51), GSE33630 (N=45, T=49), GSE53157 (N=3, T=15), GSE58545 (N=18, T=27) and GSE60542 (N=30, T=33).

## Comparison of TREM-1 Expression Between PTC and Normal Thyroid Tissues

TREM-1 mRNA expression in PTC and normal thyroid tissues was compared based on TCGA data. We defined the top quartile based on the mRNA expression rank in the THCA dataset as the H-TREM-1 group, and the remaining samples were defined as the L-TREM-1 group. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic efficacy of TREM-1. The diagnostic value of TREM-1 was further verified in 6 GEO datasets (GSE3467, GSE27155, GSE33630, GSE53157, GSE58545 and GSE60542).

Additionally, direct comparison of TREM-1 protein expression between PTC and normal thyroid tissues was performed by using immunohistochemical images from the Human Protein Atlas (https://www.proteinatlas.org).

## Analysis of the Potential Mechanism of TREM-1 in PTC

### LinkedOmics Database Analysis

LinkedOmics is an online website for analyzing multiomics data within and across 32 cancer types (http://www.linkedomics.org/) (19). Pearson correlation coefficient values were used to analyze TREM-1 coexpression, and the results were visualized with a volcano plot and heatmap. The functional modules of LinkedOmics were based on the RNA-seq and methylation data of TREM-1. In addition, gene set enrichment analysis (GSEA) was performed for gene ontology (GO) biological process terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. We used a weighted set cover approach for redundancy reduction, and we set the minimum number of genes to 10 and the number of simulations to 1000. In addition, we investigated the relationships between TREM-1 expression and gene mutations in PTC as well as between TREM-1 methylation and clinical parameters.

### Protein-protein Interaction (PPI) Network Analysis

The 100 genes with the most significant coexpression with TREM-1 in LinkedOmics were input into String (version 11.0, https://string-db.org/) to analyze the interaction network of the encoded proteins. The minimum required interaction score was 0.7 (high confidence), and the results were visualized with Cytoscape (v3.7.2).

## Analysis of the Relationship Between TREM-1 and Immune Infiltration in PTC

### ESTIMATE

Using ESTIMATE (20)to evaluate the immune cell infiltration level (immune score), matrix content (stromal score), comprehensive score (ESTIMATE score) and tumor purity of each THCA sample, we compared the tumor microenvironment among patients with different TREM-1 expression levels.

### TIMER

The TIMER online database (21) was used to analyze and visualize the associations between TREM-1 and 6 subtypes of tumor-infiltrating immune cells [B cells, CD4+ T cells, CD8+T cells, macrophages, neutrophils and dendritic cells (DCs)]. Purity-corrected partial Spearman-correlation coefficients were calculated.

### TISIDB

We used TISIDB, a web portal for analyzing tumor and immune system interactions (22), to analyze the Spearman correlation between TREM-1 expression and 28 types of tumor-infiltrating lymphocytes (TILs), immunomodulators (immunoinhibitors, immunostimulators and MHCs), chemokines and receptors as well as tumor stage and overall survival (OS) across human cancers.

### CIBERSORT

CIBERSORT (23) is a deconvolution algorithm that uses RNA-seq data to calculate the composition ratio of 22 immune cells in each blood or tissue sample. We performed 1,000 permutations and kept samples with $p$ <0.05 to ensure the accuracy of the results, and the sum of various immune cells was 1. In this study, CIBERSORT was used to analyze the Spearman correlation between TREM-1 expression and the proportion of various immune cells in THCA.

### Immune Cell Abundance Identifier (ImmuCellAI)

ImmuCellAI (24) (http://bioinfo.life.hust.edu.cn/web/ImmuCellAI/) is a method based on single sample gene set enrichment analysis (ssGSEA), which can be used to accurately estimate the abundance of 24 immune cells from gene expression data, including 18 T cell subgroups. We used ImmuCellAI to analyze the Spearman correlation between TREM-1 expression and the abundance of various immune cells in THCA.

## Analysis of TREM-1 Methylation in PTC

Based on DNA methylation data downloaded from TCGA, we compared the methylation levels of TREM-1 between PTC and normal tissues. In addition, we performed Spearman correlation analysis to assess the correlations between TREM-1 expression and methylation at each methylation site in the TREM-1 gene. The remaining methylation analysis was performed by LinkedOmics.

## Gene Expression Profiling Interactive Analysis (GEPIA)

We used the online pan-cancer analysis platform, GEPIA (http://gepia.cancer-pku.cn/) (25), to analyze the differences in TREM-1 expression levels between tumors and normal tissues across human cancers (P-value <0.05 and |logFC| >1) and the association of TREM-1 expression with pan-cancer OS.

## Statistical Analysis

The Chi-square test was used to assess differences in clinical parameters between the L-TREM-1 and H-TREM-1 groups. The Spearman method was used to test correlations. The Mann-Whitney test was used to compare data between two groups. The log-rank method was used to calculate significant P values in the survival analysis. The R software (v3.6.0) and SPSS software (v25.0) were used for statistical processing. Data visualization was performed with GraphPad Prism V.8.0 and R software.

# RESULTS

## Diagnostic Value of TREM-1 in PTC

We initially evaluated TREM-1 mRNA levels in PTC tissues from TCGA. Comparison of normal thyroid tissues (n=58) and PTC tissues (n=512) revealed that TREM-1 mRNA expression was significantly higher in PTC tissues than in normal tissues (P<0.0001) (**Figure 1A**). ROC curve analysis was performed to evaluate the diagnostic value of TREM-1 (**Figure 1B**). Additionally, the immunohistochemical results indicated that TREM-1 protein expression was much higher in PTC tissues than in normal tissues (**Figure 1C**). Furthermore, we analyzed gene expression data from 6 GEO cohorts, and all results supported the above conclusion [GSE3467 (P<0.0001), GSE27155 (P<0.0001), GSE33630 (P<0.0001), GSE58545 (P<0.05), GSE53157 (P<0.0001) and GSE60542 (P<0.0001)] (**Figures 1D–I**). ROC curve analysis was performed to evaluate the diagnostic value of TREM-1 using data from GEO cohorts (**Figures 1J–O**). The areas under the ROC curve (AUCs) were 0.8407, 1.000, 1.000, 0.9048, 0.9333, 0.9414, and 0.9000 in the seven cohorts, suggesting that TREM-1 is a potential biomarker for distinguishing PTC cases from normal controls.

## Prognostic Value of TREM-1 in PTC

Univariate and multivariate analyses of TCGA cohort were conducted to assess the prognostic value of TREM-1 (**Table 1**). Univariate analysis revealed that age (per year of age), clinical stage, tumor mutation burden (TMB) and TREM-1 expression

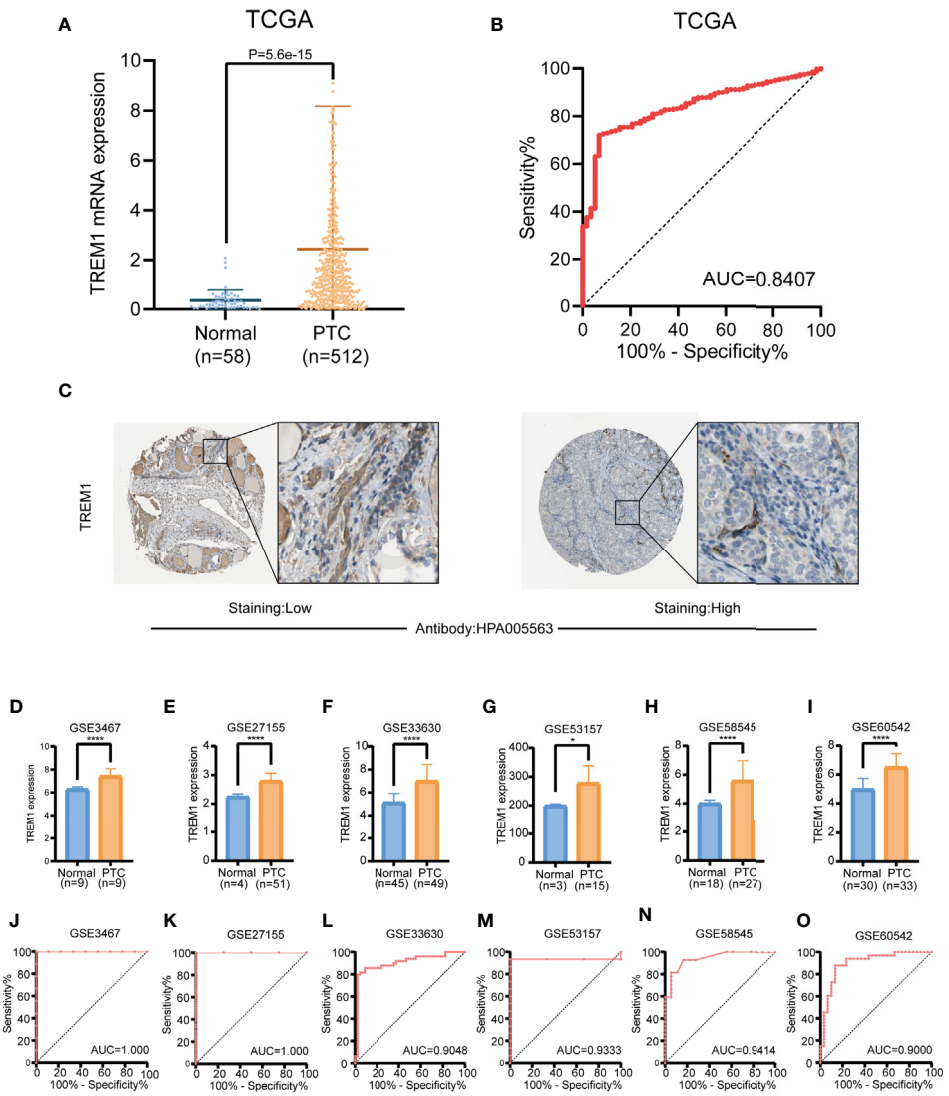


**FIGURE 1** | Diagnostic value of TREM-1 in PTC. **(A)** Comparison of TREM-1 mRNA expression between PTC and normal tissues in TCGA. **(B)** Diagnostic efficacy of TREM-1 as shown by the ROC curve. **(C)** Comparison of immunohistochemical images indicating TREM-1 expression in PTC and normal thyroid tissues. **(D–I)** TREM-1 mRNA expression in the six GEO verification cohorts (GSE3467, GSE27155, GSE33630, GSE58545, GSE53157 and GSE60542). **(J–O)** ROC curve showing the diagnostic performance of TREM-1 expression in the verification cohorts. *P < 0.05, ****P < 0.0001 here.

**TABLE 1** | Results of univariate and multivariate logistic regression analysis.

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | Hazard ratio (95%CI) | P value | Hazard ratio (95% CI) | P value |
| Age | 1.035(1.017–1.053) | <0.001 | 1.014(0.990–1.039) | 0.267 |
| Sex | 1.398(0.771–2.536) | 0.27 | 1.232(0.663–2.290) | 0.509 |
| Clinical stage | 1.739(1.367–2.212) | <0.001 | 1.429(1.048–1.948) | 0.024 |
| TMB | 2.963(1.636–5.367) | <0.001 | 1.388(0.633–3.043) | 0.412 |
| TREM-1 | 1.042(1.024–1.061) | <0.001 | 1.032(1.012–1.053) | 0.001 |

are significant risk factors for progression-free survival (PFS) (P<0.001). Multivariate analysis further revealed that high TREM-1 expression is an independent prognostic biomarker for poor PFS [hazard ratio (HR) = -1.032; 95% CI 1.012-1.053].

## Relationship of TREM-1 Expression With Clinical Parameters

The PTC patients in TCGA cohort were separated into two groups according to TREM-1 expression level (H-TREM-1 and

L-TREM-1). Comparison of the two groups indicated significant differences in the N and T classification between the groups (P<0.01). In addition, the H-TREM-1 group included more patients with classical and tall cell types but fewer patients with follicular type cells (P<0.01). Notably, high TREM-1 expression was significantly associated with lymph node metastasis and advanced T classification (**Table 2**).

## TREM-1-Related Genes in PTC

To gain insights into the biological meaning of TREM-1 in PTC, the functional module in LinkedOmics was used to examine the TREM-1 coexpression mode in the THCA cohort. A total of 9616 genes showed significant positive correlations with TREM-1, whereas 10312 genes showed significant negative correlations [false discovery rate (FDR) < 0.01] (**Figure 2A**). The top 50 genes with the most significant positive and negative correlations with TREM-1 are shown in the heat map, respectively (**Figures 2B, C**). Moreover, we constructed a PPI network with 43 hub genes and found that ITGAM plays a key role (**Figure 2D**). Regarding the relationship between TREM-1 and mutations in other genes, mutations in BRCA2 and BRAF were most closely related to TREM-1 (**Figure S1A**). Furthermore, TREM-1 expression levels in the BRAF mutant group were significantly higher than that in the BRAF wild-type group (**Figure S1B**).

**TABLE 2** | Association between TREM-1expression and clinical parameters.

| Clinical parameter | L-TREM-1 (n=376, %) | H-TREM-1 (n=125, %) | P value |
|---|---|---|---|
| Age (y) | | | |
| <55 | 248 (66.0) | 86 (68.8) | 0.559 |
| ≥55 | 128 (34.0) | 39 (31.2) | |
| Sex | | | |
| Female | 281 (74.7) | 85 (68.0) | 0.142 |
| Male | 95 (25.3) | 40 (32.0) | |
| Clinical stage | | | |
| I | 219 (58.6) | 62 (49.6) | 0.06 |
| II | 42 (11.2) | 10 (8.0) | |
| III | 73 (19.5) | 38 (30.4) | |
| IV | 40 (10.7) | 15 (12.0) | |
| NA | | | |
| Metastasis stage | | | |
| M0 | 209 (97.2) | 73 (96.1) | 0.617 |
| M1 | 6 (2.8) | 3 (3.9) | |
| NA | 161 | 49 | |
| N stage | | | |
| N0 | 186 (55.2) | 43 (37.7) | 0.001 |
| N1 | 151 (44.8) | 71 (62.3) | |
| NA | 39 | 11 | |
| T stage | | | |
| T1 | 117 (31.2) | 25 (20.2) | 0.003 |
| T2 | 130 (34.7) | 34 (27.4) | |
| T3 | 112 (29.9) | 58 (46.8) | |
| T4 | 16 (4.3) | 7 (5.6) | |
| NA | 1 | 1 | |
| Pathologic type | | | |
| Classical | 260 (69.1) | 95 (76.0) | <0.001 |
| Follicular | 89 (23.7) | 12 (9.6) | |
| Tall cell variant | 19 (5.1) | 17 (13.6) | |
| Other | 8 (2.1) | 1 (0.8) | |
| BRAF | | | |
| Wild-type | 149 (41.5) | 46 (37.7) | 0.46 |
| Mutated | 210 (58.5) | 76 (62.3) | |
| NA | 17 | 3 | |
| RAS | | | |
| Wild-type | 310 (86.4) | 111 (91.0) | 0.181 |
| Mutated | 49 (13.6) | 11 (9.0) | |
| NA | 17 | 3 | |

## Functional Enrichment Analysis of TREM-1

Annotation of significantly enriched GO terms by GSEA showed that genes coexpressed with TREM-1 were primarily involved in functions described by the following terms: adaptive immune response; neutrophil-mediated immunity; positive regulation of leukocyte activation; regulation of leukocyte activation; immune response-regulating signaling pathway; and I-kappaB kinase/NF-kappaB signaling. In contrast, activities related to the following terms were inhibited: nucleoside bisphosphate metabolic process; cellular amino acid metabolic process; ncRNA processing; and cilium organization (**Figure 2E**). KEGG pathway analysis showed enrichment of these genes in the following pathways: complement and coagulation cascades; cell adhesion molecules (CAMs); cytokine-cytokine receptor interaction; phagosome; natural killer cell mediated cytotoxicity; and chemokine signaling pathway (**Figure 2F**).

## Relationship of TREM-1 Expression With Immune Infiltration

The stromal score, immune score, ESTIMATE score and tumor purity data for TCGA cohort were obtained and compared between the H-TREM-1 and L-TREM-1 groups (**Figures 3A–D**). The H-TREM-1 group had a higher stromal score (P<0.0001) and ESTIMATE score but a lower tumor score (P<0.0001) and tumor purity (P<0.0001). Correlation analysis of TREM-1 expression with tumor purity revealed that TREM-1 may influence the immune status of the tumor microenvironment. Moreover, we investigated whether TREM-1 expression is correlated with immune infiltration in PTC *via* the TIMER database. TREM-1 expression was significantly correlated with tumor purity (r=-0.102, P<0.05) and the infiltration levels of the dominant immune cells (**Figure 3E**). Specifically, TREM-1 expression was significantly correlated with the infiltration levels of dendritic cells, neutrophils and CD8+T cells. In addition, TISIDB analysis suggested that TREM-1 expression was positively correlated with the levels of 28 TIL types (**Figure 3F**) and immunostimulators (**Figure 3G**) across human cancers and that these correlations were particularly significant in THCA. In addition, correlations between TREM-1 expression and the levels of immunoinhibitors, MHCs, chemokines and receptors were analyzed (**Figure S2**).

## Relationship of TREM-1 Expression With Various Immune Cells

To further explore the relationship between TREM-1 expression levels and the immune system, we used CIBERSORT to examine the relationship between TREM-1 expression levels and the proportion of different immune cells in PTC tissue, as well as ImmuCellAI to examine the relationship between TREM-1 expression levels and various immune cell abundances in PTC tissues. The findings (**Figure 4**) revealed that TREM-1 over-expression was related to a higher proportion of resting dendritic cells, activated dendritic cells, neutrophils, monocytes, Tregs and resting memory CD4+ T cells (P<0.05), while TREM-1 over

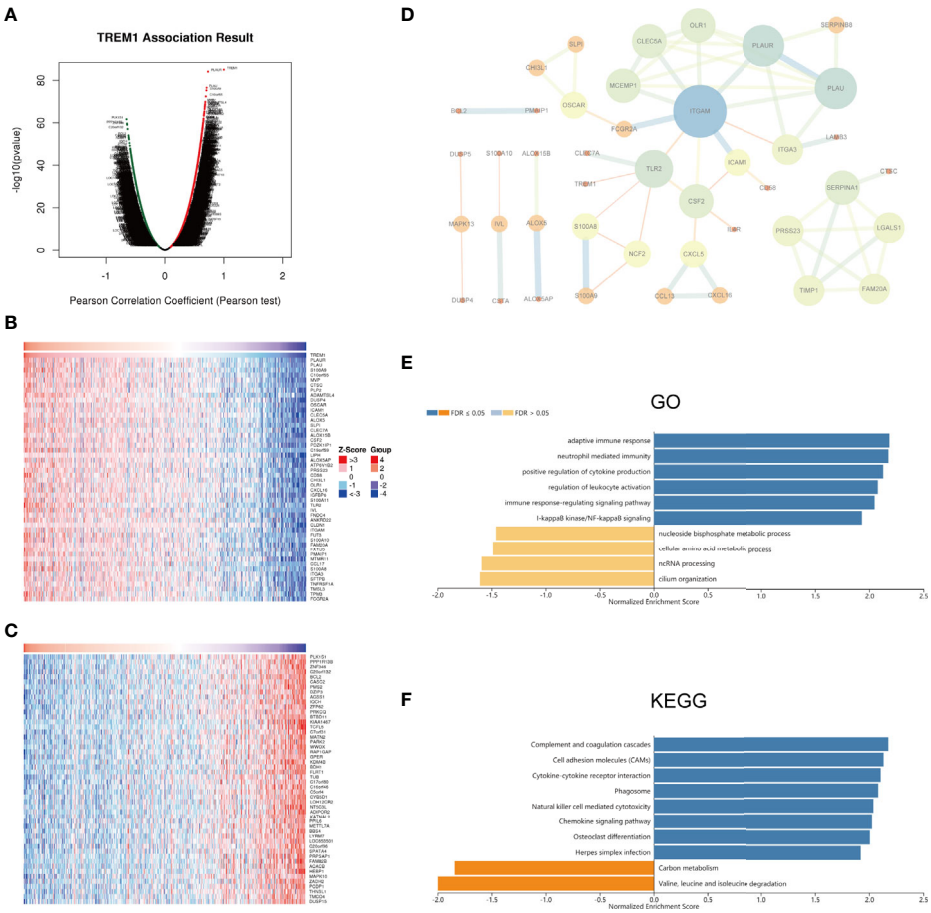


**FIGURE 2** | Potential mechanisms of TREM-1 in PTC. **(A)** Genes highly correlated with TREM-1 identified by Pearson correlation analysis in the THCA cohort. **(B)** Heatmaps showing the top 50 genes positively and **(C)** negatively correlated with TREM-1 in the TCHA cohort. **(D)** PPI of the top 100 significantly correlated genes. **(E)** GO biological process terms and **(F)** KEGG pathways significantly enriched in genes coexpressed with TREM-1 in the THCA cohort.

expression is related to a decline in the proportion of T cells gamma delta, resting NK cells, CD8+ T cells, and eosinophils (P<0.05) (**Table S1**). TREM-1 over expression was also associated with a higher abundance of dendritic cells, macrophages, monocytes, nTregs, iTregs, Tr1, Tfh, cytotoxic T cells, exhausted T cells, Th1, Th2, effector memory T cells and CD8+ T cells (P<0.05) and a lower abundance of naive CD4+ T cells, neutrophils, naive CD8+ T cells, central memory T cells, Th17, T cells gamma delta, B cells and CD4+ T cells (P<0.05) (**Table S2**). The results reflect that TREM-1 expression has a stronger correlation with innate immune cells.

## DNA Methylation of TREM-1

We performed Pearson correlation analysis to assess the correlation between TREM-1 expression and TREM-1 DNA methylation based on DNA methylation data from patients with PTC downloaded from TCGA (**Figure 5A**). The methylation level of TREM-1 DNA was significantly negatively correlated with TREM-1 mRNA expression levels (r=-0.7113, P<0.0001). Methylation at DNA TREM-1 methylation sites, including cg21328082, cg10981439, cg09310966, cg06196379, c18505453, cg03843170, cg04451353 and cg17430214, exhibited the most significant negative correlations with TREM-1 expression levels (**Table 3**). Additionally, the methylation level of TREM-1 in PTC tissues was significantly lower than in normal tissues (P<0.0001) (**Figure 5B**). Therefore, we hypothesized that DNA methylation may be the upstream mechanism regulating TREM-1 in PTC. Patients were classified according to clinical

**TABLE 3** | Spearman correlation between TREM-1 methylation sites and TREM-1 expression.

| Methylation site | Spearman r | P value |
|---|---|---|
| cg21328082 | -0.679 | 3.49E-69 |
| cg10981439 | -0.581 | 1.13E-46 |
| cg09310966 | -0.447 | 5.07E-26 |
| cg06196379 | -0.41 | 9.42E-22 |
| cg18505453 | -0.289 | 4.16E-11 |
| cg03843170 | -0.188 | 2.14E-05 |
| cg04451353 | -0.105 | 1.90E-02 |
| cg17430214 | NA | NA |

*NA, Not applicable.*

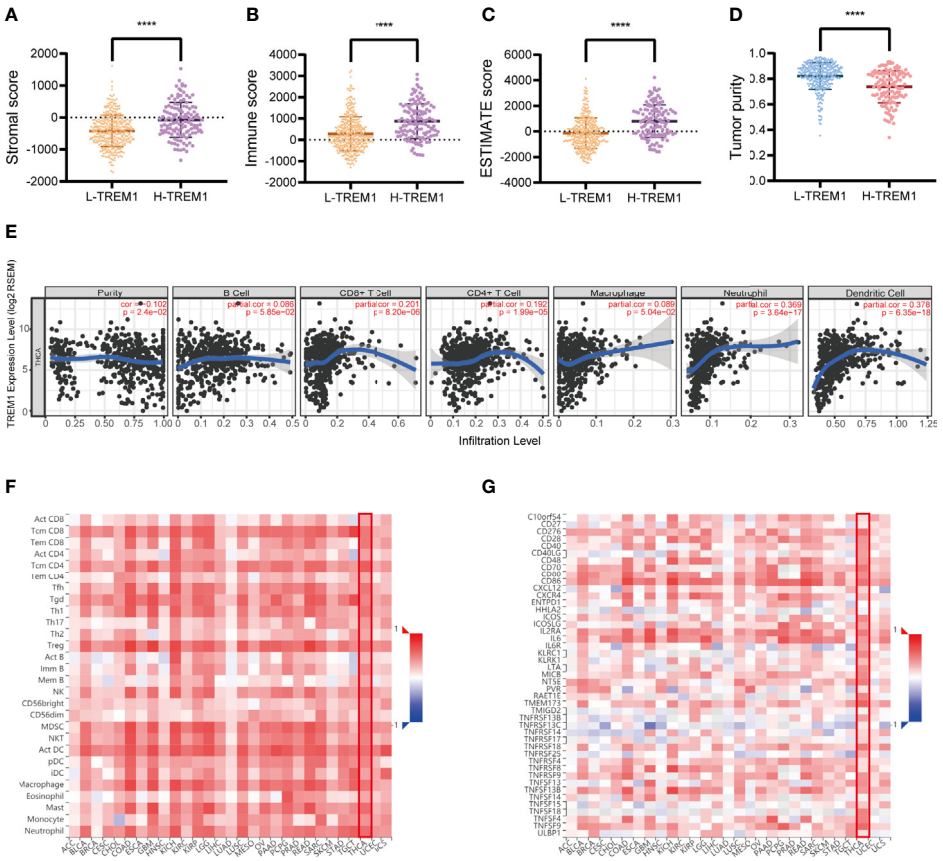


**FIGURE 3** | TREM-1 is closely related to immunity in PTC. ESTIMATE analysis of **(A)** stromal scores, **(B)** immune scores, **(C)** ESTIMATE scores and **(D)** tumor purity between the L-TREM-1 and H-TREM-1 groups. **(E)** TIMER analysis of purity-corrected partial Spearman correlations between the expression of TREM-1 and the infiltration of 6 types of immune cells in the THCA cohort. **(F)** Correlation analysis between the expression of TREM-1 and 28 types of TILs across human cancers *via* TISIDB. **(G)** Correlation analysis between the expression of TREM-1 and the levels of immunostimulators across human cancers *via* TISIDB. ****P < 0.0001 here.

indicators, and we compared their TREM-1 methylation levels (**Figures 5C–F**). Lower methylation levels of TREM-1 were found in patients with advanced clinical stage, advanced T classification, advanced N classification and tall cell variant PTC. To understand the biological significance of TREM-1 methylation in THCA, a functional module of LinkedOmics was used to examine TREM-1 coexpression patterns in the THCA cohort. Using RNAseq, we screened 19928 genes related to TREM-1 methylation (false discovery rate (FDR) <0.01). The GO (biological process) analysis results derived by GSEA were significant. The results indicated that TREM-1 methylation-coexpressed genes primarily participate in generation of precursor metabolites and energy, ncRNA processing, cilium organization, and small molecule catabolic process, while extracellular structure organization, positive regulation of defense response, adaptive immune response, cell-cell adhesion *via* plasma-membrane adhesion molecules, granulocyte activation and leukocyte migration were inhibited (**Figure 5G**). KEGG pathway analysis showed that genes related to carbon metabolism, aminoacyl-tRNA biosynthesis, and thermogenesis were activated, while phagosome, chemokine signaling pathway, osteoclast differentiation, transcriptional misregulation in cancer, cytokine-cytokine receptor interaction, complement and coagulation cascades and cell adhesion molecules (CAMs) were inhibited (**Figure 5H**).

## Generalization Value of TREM-1 Across Cancers

To investigate whether TREM-1 has broad value across cancers, we performed a series of studies on TREM-1 in a pan-cancer cohort. GEPIA showed that the TREM-1 expression status varied across cancers (**Figure 6A**). TISIDB analysis showed that high expression of TREM-1 in the pan-cancer cohort was accompanied by a more advanced tumor stage (**Figure 6B**) and shorter OS time (**Figure 6C**). Kaplan-Meier (K-M) survival analysis showed that the high TREM-1 groups in the cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), glioblastoma multiforme (GBM), kidney renal clear cell carcinoma (KIRC), brain lower grade glioma (LGG), liver hepatocellular carcinoma (LIHC), lung squamous cell carcinoma (LUSC) and pancreatic adenocarcinoma (PAAD) cohorts had significantly shorter OS times (**Figures 6D–J**). The difference was the most significant in

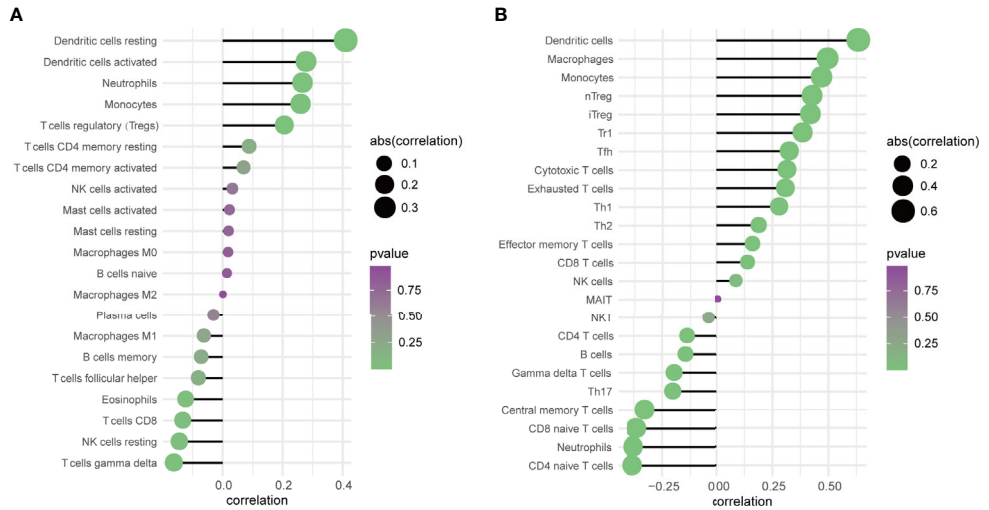


**FIGURE 4** | The relationship between TREM-1 and immune cells in PTC. **(A)** Correlation analysis between TREM-1 expression and the proportion of immune cells in PTC (CIBERSORT, n=259). **(B)** Correlation analysis between TREM-1 expression and the abundance of immune cells in PTC (ImmuCellAI, n=512).

the survival statistics of a large sample in the pan-cancer cohort (N = 9502, HR = 1.7, P <0.0001) (**Figure 6K**).

## DISCUSSION

The present study utilized PTC patient sequencing data in public databases and presented the first report of the expression level and biological function of TREM-1 in PTC. The expression level of TREM-1 in PTC tissues was significantly higher than that in noncancerous thyroid tissues at both the transcriptional and translational levels. Furthermore, our results indicated the prognostic and diagnostic value of TREM-1. Our findings suggest a clinical correlation of disease severity and subclassification with gene expression levels, indicating that TREM-1 may affect disease progression. Previous research has identified a significant correlation between TREM-1 mRNA expression and TREM-1 DNA methylation levels (26). Our TREM-1 methylation analysis data also implied that DNA methylation is an epigenetic regulatory mechanism of TREM-1 resulting in transcriptional silencing. The finding of TREM-1 hypomethylation also validated its high protein levels in PTC and its effect on disease progression. Our results suggested that the functional consequences of TREM-1 mainly include effects on immune-related responses. Therefore, we adopted the ESTIMATE and TIMER algorithms to investigate the infiltration of immune cells and found that TREM-1 expression is associated with tumor-infiltrating immune cells, and exhibited positive associations with immune infiltration of dendritic cells, neutrophils and CD8+T cells. TREM-1 has extensive prognostic value in pan-cancer.

TREM-1 is expressed at late stages of myeloid cell differentiation (27) and is found on monocytes/macrophages and neutrophils with high CD14 expression (7). TREM-1 acts as an important mediator of intracellular signaling by immune cells during physiological processes and plays an important role in the triggering and amplification of the inflammatory response. The interaction of cancer cells with inflammatory cells, in addition to cytokine responses, in the tumor microenvironment may contribute to tumor growth, progression and immunosuppression (28). Therefore, we reasoned that TREM-1 may participate in carcinogenesis *in vivo* mainly through immune-related mechanisms.

Duan et al. (11) showed that TREM-1 induces the expression and secretion of various cytokines and chemokines, thereby promoting the development of the tumor microenvironment and ultimately contributing to tumor progression. These researchers revealed that TREM-1 overexpression upregulates the secretion of IL-1, IL-6, IL-8, MCP-1, MCP-3, MIP-1, TNF-a, GM-CSF, MPO, and VEGF but decreases the secretion of IL-10. We also found positive correlations between TREM-1 and IL-6 (**Figure 3G**), IL-8 (**Figure S2C**, shown as CXCL8), MCP-1 (**Figure S2C**, shown as CCL2), the GM-CSF receptor (**Figure S2A**, shown as CSF1R) and IL-10 (**Figure S2A**). In addition, the expression of the TNF-α receptor, TNFRSF1A, was significantly and positively correlated with TREM-1 expression (**Figure 2B**). Immune infiltration is associated with PTC and may play a critical role in carcinogenesis regulation and carcinoma progression (29). Therefore, we hypothesized that in PTC, TREM-1 induces cytokine expression and produces an inflammatory microenvironment. Long-term inflammatory damage induces cell renewal and repair of defective tissues. During the repair process, carcinogens or macrophages can cause DNA damage in cells, and cell proliferation and differentiation become disordered, establishing conditions supporting tumor formation and metastasis.

The metastatic potential of primary tumors can be enhanced *via* exploitation of aberrant immune cell crosstalk (30). Infiltration of immune cells in tumors modulates the local

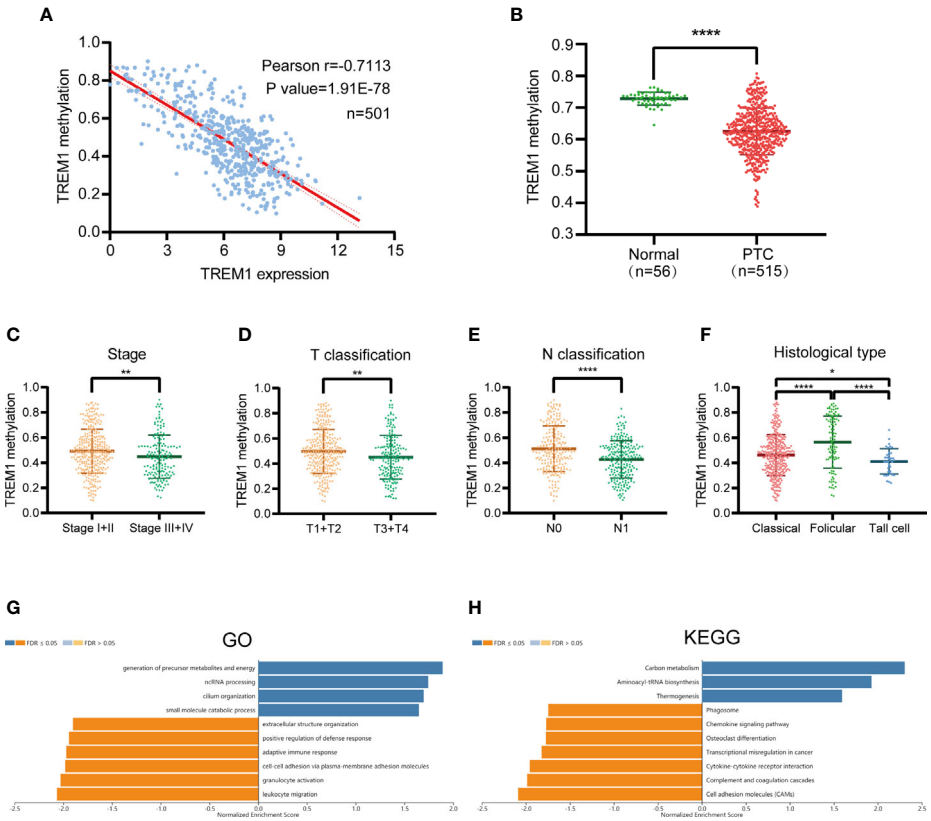


**FIGURE 5** | TREM-1 Methylation in PTC. **(A)** Correlation analysis between TREM-1 methylation and TREM-1 expression in PTC **(B)** TREM-1 methylation levels were compared between PTC and normal tissues. TREM-1 methylation level among patients with different **(C)** clinical stages, **(D)** T classifications, **(E)** N classifications and **(F)** histological types of PTC. **(G)** GO biological process terms and **(H)** KEGG pathways significantly altered by TREM-1 methylation in the THCA cohort. *P < 0.05, **P < 0.01 and ****P < 0.0001 here.

microenvironment and influences cancer progression and the therapeutic response. Our study showed that TREM-1 is significantly correlated with the infiltration of several immune cells (**Figure 3E**). Furthermore, correlation analysis between TREM-1 expression and 28 types of TILs across human cancers revealed that TREM-1 may participate in complicated immune cell crosstalk, possibly explaining why TREM-1 is closely related to lymph node metastasis in PTC.

Triggering receptor expressed on myeloid cells-2 (TREM-2) is another member of the TREM family. Opposite to TREM-1, TREM-2 functions as an anti-inflammatory modulator and phagocytic promoter (31). A previous study on melanoma found that the increased ratio of TREM-1 to TREM-2 may promote the pro-inflammatory and pro-tumor state of the tumor microenvironment (32). This evidence suggests a TREM-1/TREM-2 paradigm in which the relative levels of these two TREM family members, instead of the absolute expression levels of one or the other, dictate inflammatory and immune status, which provides a novel approach for TREM-1 functional studies in PTC.

TREM-1 is expressed as a transmembrane receptor complex with the DAP12 chain subunit. TREM-1 signaling activates the RAS gene, activates the mitogen-activated protein kinase (MAPK) pathway and mediates ERK phosphorylation (9). The RAS gene is the most common target for acquired somatic function mutations in human cancer (33). Oncogenic activation of BRAF enhances cancer progression by constitutively promoting RAS-independent MAPK pathway signaling (1). The BRAF V600E mutation is the most prevalent oncogenic mutation in PTC, occurring in an average of 45% of patients (34). As the TREM-1 expression level showed a significant correlation with BRAF mutation and the degree of PTC severity in our study, we assumed that the mechanism underlying this deterioration may be a synergistic interaction between TREM-1 and BRAF *via* MAPK pathway activation.

## CONCLUSIONS

The identification of TREM-1 expression alterations in PTC tissues is an important step toward improving our understanding of PTC pathogenesis and identifying new therapeutic and biomarker targets. Several mechanisms have been proposed to explain the possible role of TREM-1 in PTC development.

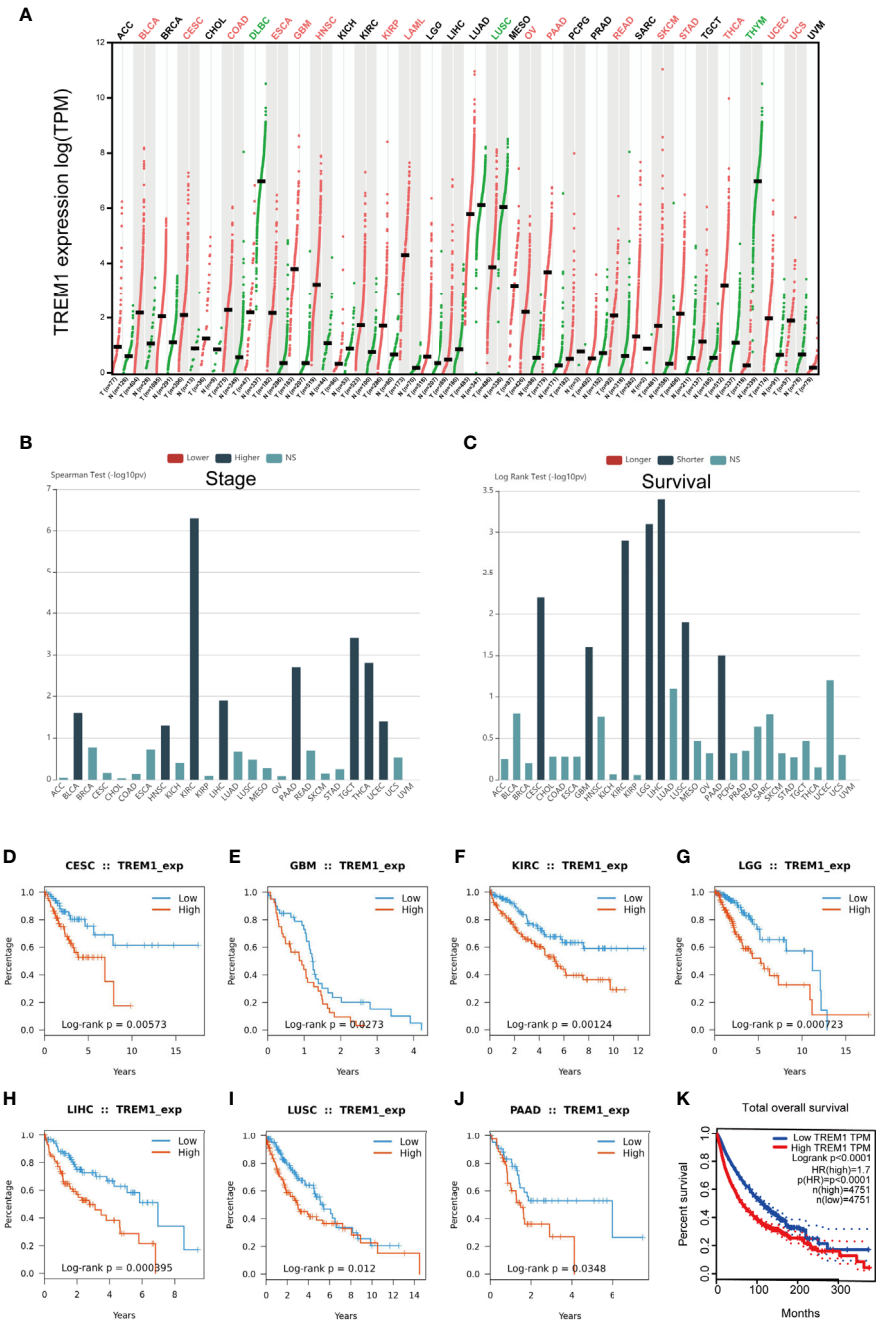


**FIGURE 6** | Generalization value of TREM-1 across cancers. **(A)** Comparison of TREM-1 mRNA expression between cancer and paracancerous tissues across cancers. **(B)** Associations between TREM-1 expression and stage across human cancers. **(C)** Associations between TREM-1 expression and OS across human cancers. K-M survival analysis between the L-TREM-1 and H-TREM-1 groups in the **(D)** CESC, **(E)** GBM, **(F)** KIRC, **(G)** LGG, **(H)** LIHC, **(I)** LUSC, **(J)** PAAD and **(K)** pan-cancer cohorts.

Although the molecular functions of TREM-1 in PTC have been analyzed using bioinformatics approaches, the conclusions have not been confirmed by experiments, and related experimental research is ongoing.

## DATA AVAILABILITY STATEMENT

Publicly available datasets were used in this study. Details can be found in the manuscript.

## AUTHOR CONTRIBUTIONS

ZX designed the analytical strategies, performed data analyses and wrote the manuscript. XL performed data analysis and wrote the manuscript. YZH, SW, SYW, JS, YCH, and YL performed data analysis. JZ conceived the research and wrote the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

This research was supported by the National Natural Science Foundation of China (81600602).

## ACKNOWLEDGMENTS

We would like to acknowledge the public databases including TCGA and GEO for their contributions to human medicine.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.646793/full#supplementary-material

**Supplementary Figure 1 |** Relationship between TREM-1 expression and gene mutations in PTC. **(A)** Volcano plot of TREM-1 expression and gene mutations in THCA. **(B)** Relationship between TREM-1 expression and *BRAF* mutation.

**Supplementary Figure 2 |** TREM-1 expression is closely related to immunity across human cancers. Correlation analysis between TREM-1 expression and the levels of **(A)** immunoinhibitors, **(B)** MHCs, **(C) c**hemokines and **(D)** receptors across human cancers *via* TISIDB.

**Supplementary Table 1 |** Association between TREM-1 expression and immune cell proportions.

**Supplementary Table 2 |** Association between TREM-1 expression and immune cell abundences.

## REFERENCES


1. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF Gene in Human Cancer. *Nature* (2002) 417(6892):949–54. doi: 10.1038/nature00766
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global Cancer Statistics. *CA Cancer J Clin* (2011) 61(2):69–90. doi: 10.3322/caac.20107
3. Kitahara CM, Sosa JA. The Changing Incidence of Thyroid Cancer. *Nat Rev Endocrinol* (2016) 12(11):646–53. doi: 10.1038/nrendo.2016.110
4. Yu QA, Ma DK, Liu KP, Wang P, Xie CM, Wu YH, et al. Clinicopathologic Risk Factors for Right Paraesophageal Lymph Node Metastasis in Patients With Papillary Thyroid Carcinoma. *J Endocrinol Invest* (2018) 41(11):1333–8. doi: 10.1007/s40618-018-0874-4
5. Xing M. Molecular Pathogenesis and Mechanisms of Thyroid Cancer. *Nat Rev Cancer* (2013) 13(3):184–99. doi: 10.1038/nrc3431
6. Ford JW, McVicar DW. TREM and TREM-like Receptors in Inflammation and Disease. *Curr Opin Immunol* (2009) 21(1):38–46. doi: 10.1016/j.coi.2009.01.009
7. Bouchon A, Dietrich J, Colonna M. Cutting Edge: Inflammatory Responses can be Triggered by TREM-1, a Novel Receptor Expressed on Neutrophils and Monocytes. *J Immunol* (2000) 164(10):4991–5. doi: 10.4049/jimmunol.164.10.4991
8. Bouchon A, Facchetti F, Weigand MA, Colonna M. TREM-1 Amplifies Inflammation and is a Crucial Mediator of Septic Shock. *Nature* (2001) 410 (6832):1103–7. doi: 10.1038/35074114
9. Colonna M. Trems in the Immune System and Beyond. *Nat Rev Immunol* (2003) 3(6):445–53. doi: 10.1038/nri1106
10. Ho CC, Liao WY, Wang CY, Lu YH, Huang HY, Chen HY, et al. TREM-1 Expression in Tumor-Associated Macrophages and Clinical Outcome in Lung Cancer. *Am J Respir Crit Care Med* (2008) 177(7):763–70. doi: 10.1164/rccm.200704-641OC
11. Duan M, Wang ZC, Wang XY, Shi JY, Yang LX, Ding ZB, et al. Trem-1, an Inflammatory Modulator, is Expressed in Hepatocellular Carcinoma Cells and Significantly Promotes Tumor Progression. *Ann Surg Oncol* (2015) 22 (9):3121–9. doi: 10.1245/s10434-014-4191-7
12. Liao R, Sun TW, Yi Y, Wu H, Li YW, Wang JX, et al. Expression of TREM-1 in Hepatic Stellate Cells and Prognostic Value in Hepatitis B-related Hepatocellular Carcinoma. *Cancer Sci* (2012) 103(6):984–92. doi: 10.1111/j.1349-7006.2012.02273.x
13. Zhu R, Guo W, Xu XJ, Zhu L. An Integrating Immune-Related Signature to Improve Prognosis of Hepatocellular Carcinoma. *Comput Math Methods Med* (2020) 2020:8872329. doi: 10.1155/2020/8872329
14. Kim SK, Kim SY, Kim JH, Roh SA, Cho DH, Kim YS, et al. A Nineteen Gene-Based Risk Score Classifier Predicts Prognosis of Colorectal Cancer Patients. *Mol Oncol* (2014) 8(8):1653–66. doi: 10.1016/j.molonc.2014.06.016
15. Schulz A, Toedt G, Zenz T, Stilgenbauer S, Lichter P, Seiffert M. Inflammatory Cytokines and Signaling Pathways are Associated With Survival of Primary Chronic Lymphocytic Leukemia Cells In Vitro: A Dominant Role of CCL2. *Haematologica* (2011) 96(3):408–16. doi: 10.3324/haematol.2010.031377
16. Cioni B, Zaalberg A, van Beijnum JR, Melis MHM, van Burgsteden J, Muraro MJ, et al. Androgen Receptor Signalling in Macrophages Promotes TREM-1-mediated Prostate Cancer Cell Line Migration and Invasion. *Nat Commun* (2020) 11(1):4498. doi: 10.1038/s41467-020-18313-y
17. Singh H, Rai V, Nooti SK, Agrawal DK. Novel Ligands and Modulators of Triggering Receptor Expressed on Myeloid Cells Receptor Family: 2015-2020 Updates. *Expert Opin Ther Pat* (2021), 1–13. doi: 10.1080/13543776.2021.1883587
18. Raggi F, Bosco MC. Targeting Mononuclear Phagocyte Receptors in Cancer Immunotherapy: New Perspectives of the Triggering Receptor Expressed on Myeloid Cells (Trem-1). *Cancers (Basel)* (2020) 12(5). doi: 10.3390/cancers12051337
19. Vasaikar SV, Straub P, Wang J, Zhang B. LinkedOmics: Analyzing Multi-Omics Data Within and Across 32 Cancer Types. *Nucleic Acids Res* (2018) 46 (D1):D956–63. doi: 10.1093/nar/gkx1090
20. Yoshihara K, Shahmoradgoli M, Martinez E, Vegesna R, Kim H, Torres-Garcia W, et al. Inferring Tumour Purity and Stromal and Immune Cell Admixture From Expression Data. *Nat Commun* (2013) 4:2612. doi: 10.1038/ncomms3612
21. Li T, Fan J, Wang B, Traugh N, Chen Q, Liu JS, et al. Timer: A Web Server for Comprehensive Analysis of Tumor-Infiltrating Immune Cells. *Cancer Res* (2017) 77(21):e108–10. doi: 10.1158/0008-5472.CAN-17-0307
22. Ru B, Wong CN, Tong Y, Zhong JY, Zhong SSW, Wu WC, et al. TISIDB: An Integrated Repository Portal for Tumor-Immune System Interactions. *Bioinformatics* (2019) 35(20):4200–2. doi: 10.1093/bioinformatics/btz210
23. Newman AM, Liu CL, Green MR, Gentles AJ, Feng W, Xu Y, et al. Robust Enumeration of Cell Subsets From Tissue Expression Profiles. *Nat Methods* (2015) 12(5):453–7. doi: 10.1038/nmeth.3337
24. Miao Y-R, Zhang Q, Lei Q, Luo M, Xie G-Y, Wang H, et al. Immucellai: A Unique Method for Comprehensive T-Cell Subsets Abundance Prediction and its Application in Cancer Immunotherapy. *Advanced Sci (Weinheim Baden-Wurttemberg Germany)* (2020) 7(7):1902880. doi: 10.1002/advs.201902880
25. Tang Z, Li C, Kang B, Gao G, Li C, Zhang Z. GEPIA: A Web Server for Cancer and Normal Gene Expression Profiling and Interactive Analyses. *Nucleic Acids Res* (2017) 45(W1):W98–W102. doi: 10.1093/nar/gkx247
26. Sao T, Yoshino Y, Yamazaki K, Ozaki Y, Mori Y, Ochi S, et al. TREM1 Mrna Expression in Leukocytes and Cognitive Function in Japanese Patients With Alzheimer's Disease. *J Alzheimers Dis* (2018) 64(4):1275–84. doi: 10.3233/JAD-180418
27. Gomez-Pina V, Soares-Schanoski A, Rodriguez-Rojas A, Del Fresno C, Garcia F, Vallejo-Cremades MT, et al. Metalloproteinases Shed TREM-1 Ectodomain

From Lipopolysaccharide-Stimulated Human Monocytes. *J Immunol* (2007) 179(6):4065–73. doi: 10.4049/jimmunol.179.6.4065
28. Balkwill F, Mantovani A. Inflammation and Cancer: Back to Virchow? *Lancet* (2001) 357(9255):539–45. doi: 10.1016/S0140-6736(00)04046-0
29. Bozec A, Lassalle S, Hofman V, Ilie M, Santini J, Hofman P. The Thyroid Gland: A Crossroad in Inflammation-Induced Carcinoma? An Ongoing Debate With New Therapeutic Potential. *Curr Med Chem* (2010) 17 (30):3449–61. doi: 10.2174/092986710792927804
30. Garner H, de Visser KE. Immune Crosstalk in Cancer Progression and Metastatic Spread: A Complex Conversation. *Nat Rev Immunol* (2020) 20 (8):483–97. doi: 10.1038/s41577-019-0271-z
31. Sharif O, Knapp S. From Expression to Signaling: Roles of TREM-1 and TREM-2 in Innate Immunity and Bacterial Infection. *Immunobiology* (2008) 213(9-10):701–13. doi: 10.1016/j.imbio.2008.07.008
32. Nguyen AH, Koenck C, Quirk SK, Lim VM, Mitkov MV, Trowbridge RM, et al. Triggering Receptor Expressed on Myeloid Cells in Cutaneous Melanoma. *Clin Transl Sci* (2015) 8(5):441–4. doi: 10.1111/cts.12308
33. Schubbert S, Shannon K, Bollag G. Hyperactive Ras in Developmental Disorders and Cancer. *Nat Rev Cancer* (2007) 7(4):295–308. doi: 10.1038/nrc2109
34. Wang F, Zhao S, Shen X, Zhu G, Liu R, Viola D, et al. Braf V600E Confers Male Sex Disease-Specific Mortality Risk in Patients With Papillary Thyroid Cancer. *J Clin Oncol* (2018) 36(27):2787–95. doi: 10.1200/JCO.2018.78.5097

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 12 July 2021
doi: 10.3389/fendo.2021.675643

# Risk Factors for Contralateral Occult Carcinoma in Patients With Unilateral Papillary Thyroid Carcinoma: A Retrospective Study and Meta-Analysis

*Fan Zhang*[1], *Boyuan Zheng*[2], *Xiaohui Yu*[1], *Xichang Wang*[1], *Shiwei Wang*[1] *and Weiping Teng*[1]*

[1] Department of Endocrinology and Metabolism, Institute of Endocrinology, National Health Commission Key Laboratory of Diagnosis and Treatment of Thyroid Diseases, The First Hospital of China Medical University, Shenyang, China, [2] Department of Thyroid Surgery, The First Hospital of China Medical University, Shenyang, China

OPEN ACCESS

**Edited by:**
*Trevor Edmund Angell, University of Southern California, United States*

**Reviewed by:**
*Zhihong Wang, China Medical University, China*
*Wendy Sacks, Cedars Sinai Medical Center, United States*

***Correspondence:**
*Weiping Teng*
*twp@vip.163.com*

**Specialty section:**
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

**Received:** *03 March 2021*
**Accepted:** *07 June 2021*
**Published:** *12 July 2021*

**Citation:**
*Zhang F, Zheng B, Yu X, Wang X, Wang S and Teng W (2021) Risk Factors for Contralateral Occult Carcinoma in Patients With Unilateral Papillary Thyroid Carcinoma: A Retrospective Study and Meta-Analysis. Front. Endocrinol. 12:675643. doi: 10.3389/fendo.2021.675643*

**Background:** Bilateral lesions are common in papillary thyroid carcinoma (PTC). For patients with unilateral PTC, occult carcinoma that is not detected preoperatively, but pathologically after surgery, might remain in the contralateral lobe. In this situation, inadequate surgical extent could cause relapse and even lead to re-operation. Here, we explore the frequency and investigate the risk factors of contralateral occult PTC in unilateral PTC through a retrospective study conducted by our team and published articles online, respectively.

**Methods:** We collected the patients' clinical data in our hospital, whose cancer was determined to be confined to the unilateral lobe by preoperative image examination (N = 204). These patients underwent initially total or near-total thyroidectomy and included their clinical data in the meta-analysis. We searched related literature in the PubMed, Embase, MEDLINE, Cochrane, and Web of Science databases until December 7, 2020, in order to perform a meta-analysis. The relevant articles were examined and the eligible studies were included to assess the association between clinicopathologic factors and contralateral occult PTC.

**Results:** The meta-analysis included nine studies (involving 4347 patients). Of these, eight studies were from the databases, and one study was our retrospective data. The meta-analysis showed that the prevalence of contralateral occult PTC was 26.6% in all patients. A tumor size > 1 cm, ipsilateral multifocality, contralateral benign nodule, and central lymph node metastasis were significantly associated with contralateral occult PTC. In contrast, sex, age, ETE, capsular invasion, *BRAF* mutation, Hashimoto thyroiditis, and lateral lymph node metastasis were insignificantly associated with contralateral occult PTC.

**Conclusion:** The meta-analysis identified a tumor size > 1 cm, ipsilateral multifocality, contralateral benign nodule, and CLNM as being significant risk factors for contralateral occult PTC. These findings may guide the extent of surgery in unilateral PTC patients.

**Keywords: contralateral, meta-analysis, occult, papillary thyroid carcinoma, risk factors**

## INTRODUCTION

Thyroid carcinoma is the most frequent endocrine malignancy, accounting for approximately 2.9% of all newly diagnosed cancer (1). Its incidence has increased from 5.7 to 14.7 per 100,000 people over the past two decades (2). Papillary thyroid carcinoma (PTC), medullary thyroid carcinoma, follicular thyroid carcinoma, and anaplastic thyroid carcinoma are the four main types of thyroid carcinoma. PTC is the most common thyroid cancer type, accounting for approximately 80.0% of malignant thyroid tumors (3). In addition, papillary thyroid microcarcinoma (PTMC) is classified to PTC. According to the histological classification of thyroid tumors by the World Health Organization, PTMC is defined as tumors with a maximum size of 10 mm or smaller. PTC has an excellent prognosis, with the main treatment being surgical resection. The overall survival rate has remained between 90% and 96% in recent decades (4, 5).

Despite advances in the understanding of the underlying biological characteristics of PTC and the development of evidence-based guidelines for its treatment, the adequate extent of surgical management (lobectomy *vs*. total thyroidectomy) of PTC is still a matter of debate. Neck ultrasound (US) and US-guided fine-needle aspiration (FNA) are currently used in decision making for the surgical management of PTC. However, despite that high-resolution US can detect foci as small as 2 mm (6), smaller tumors remain undetected. Occult carcinoma is defined as a tumor that is not detected preoperatively but pathologically after surgery. As reported, PTC frequently occurs as multifocal or bilateral lesions, with the prevalence of multifocality ranging from 20.0% to 36.1% (7–9). The 2015 American Thyroid Association Guidelines (10) endorse thyroid lobectomy (TL) as an initial surgical approach for low risk, small- to medium-sized (T1-T2), N0 PTC in the absence of an extrathyroidal extension (ETE). For PTCs detected preoperatively in bilateral lobes, there is no controversy in performing total thyroidectomy (TT). Contralateral occult PTC is a specific subtype of bilateral multifocal PTC. It has been reported that the rate of occult PTC in the contralateral lobe ranges from 12% to 40% (11–13). For contralateral occult PTC, TL may be insufficient and could cause relapse and even lead to re-operation, which brings higher risks. Therefore, identifying risk factors of contralateral occult PTC could help surgeons to determine the optimal scope of surgery, but there is a limited number of studies focusing on risk factors of contralateral occult PTC. In this study, we used our retrospective research data and reviewed all related literature on the website that conducted this meta-analysis, aiming to estimate the risk factors for contralateral occult carcinoma in patients with unilateral PTC.

**Abbreviations:** PTC, papillary thyroid carcinoma; CLNM, central lymph node metastasis; ETE, extrathyroidal extension; HT, Hashimoto thyroiditis; LLNM, lateral lymph node metastasis; TC, thyroid carcinoma; PTMC, papillary thyroid microcarcinoma; WHO, World Health Organization; US, neck ultrasound; FNA, fine-needle aspiration; TL, thyroid lobectomy; TT, total thyroidectomy; SD, standard deviations; CIs, confidence intervals.

## MATERIALS AND METHODS

We collected the clinical data of patients with PTC treated in the First Hospital of China Medical University (Shenyang, China) from January 2016 to January 2021. Data collected included age, sex, thyroid ultrasound report, operation record, diagnosis, and pathology report. The inclusion criteria were as follows: PTC confined to the only unilateral lobe by preoperative image examinations or fine-needle aspiration cytology; patients who underwent initially total or near-total thyroidectomy; and postoperative pathological examination confirming the unilateral lesion was PTC. Also, the exclusion criteria were as follows: the patients had a suspicious lesion on the contralateral lobe; PTC located in the isthmus. Finally, 204 patients were included in our study, in which 27 patients were with contralateral occult PTC (confirmed by pathological examination). These clinical data were included in the meta-analysis.

Our meta-analysis was conducted according to the guidelines proposed by the preferred reporting items for systematic review and meta-analyses statement (14).

### Search Strategy

An electronic search of the PubMed, Embase, MEDLINE, Cochrane, and Web of Science databases was performed to identify relevant articles until December 7, 2020. We used the following search terms in "all fields": ((occult) AND (contralateral OR bilateral), AND (papillary thyroid) AND (carcinoma OR cancer OR tumor OR neoplasm)). Besides, a manual review of the references from the included studies was performed to identify additional relevant articles. Two authors independently performed the selection process, and the discrepancies were resolved by discussion. If multiple published studies illustrated the same population, we extracted the most complete or recent one.

### Selection Criteria

We included studies that met the following criteria:

1. Prospective or retrospective original studies.
2. PTC confined to only the unilateral lobe by preoperative image examinations or FNA.

3. Patients had initially undergone total or near-total thyroidectomy.
4. Pathologic examination confirming the presence of contralateral occult PTC.
5. Risk factors of contralateral occult PTC were available for extraction to calculate the pooled odds ratio (OR).

We excluded studies by the following criteria:

1. Reviews, case reports, letters to the editor, and conference abstracts.
2. Studies published in languages other than English and Chinese.
3. Studies enrolled patients with follicular thyroid carcinoma, medullary thyroid carcinoma, or anaplastic carcinoma.
4. The patients had a suspicious lesion on the contralateral lobe.
5. PTC located in the isthmus.
6. Lacked complete clinical data.

## DATA EXTRACTION AND QUALITY ASSESSMENT

Each eligible study was extracted by two independent reviewers. Disagreements were resolved by consensus or adjudication of the senior authors. We extracted the following data from the included studies: (1) study characteristics: first author, publication year, country of study, study design, study population (PTC or PTMC), number of patients, and surgical extent; (2) clinicopathologic factors for contralateral occult carcinoma: sex, age, tumor size, ipsilateral multifocality, ETE, capsular invasion, *BRAF* mutation, Hashimoto thyroiditis (HT), presence of contralateral benign nodule, central lymph node metastasis (CLNM), and lateral lymph node metastasis (LLNM).

The included studies were estimated using the Newcastle-Ottawa scale (15), which allows evaluation of cohort studies by a total of eight items of three major parts, including the study population selection, comparability, and the result. A score of 0 to 9 stars was used to assess each study. A study achieving more than six stars was considered a high-quality study. All quality assessments were performed by two independent reviewers.

## STATISTICAL ANALYSIS

The retrospective research data statistical analyses were performed using the SPSS v 26.0 software (Chicago, USA). The continuous variables are expressed as a mean ± standard deviation (SD). Univariate analysis for comparisons between patient groups was performed using Pearson's chi-square test or Fisher's exact test. Variables with a $p < 0.05$ in the univariate analysis were included in the multivariable analysis. Logistic regression analysis was performed to assess the risk factors of contralateral occult carcinoma.

We performed the meta-analysis by Revman Manager 5.0 (Cochrane Collaboration, Oxford, UK). The OR was used to compare dichotomous variables. All results were estimated with 95% confidence intervals (CIs). A P-value < 0.05 was considered statistically significant. Heterogeneity was examined by using the Q-test and $I^2$ statistic. When $p > 0.1$ and $I^2 < 50\%$, a fixed-effect model was used; otherwise, a random-effects model was applied. Possible publication bias was tested using Begg's funnel plot.

## RESULTS

### Retrospective Study

#### Patients and Tumor Characteristics

After screening the medical records, 204 patients met the criteria and were included in the study. Of these patients, 47 (23.0%) were men, and 157 (77.0%) were women. The average age was 42.5 years, and the age range was 22 to 67 years. Briefly, 172 (84.3%) patients were younger than 55 years, and 32 (15.7%) were 55 years and older. All patients underwent surgical treatment. The average tumor size was 1.28 cm, and the size range was 0.32 to 5.80 cm. In 93 (45.6%) patients, the tumor size was ≤ 1 cm; and in 111 (54.4%) patients, the tumor size was > 1 cm. For the patients included, 27 (13.2%) had contralateral occult carcinoma and 177 (13.2%) did not; 21 (10.3%) patients had ETE and 183 (89.7%) patients did not; 65 (31.9%) patients had central lymph node metastasis, 40 (19.6%) patients had lateral lymph node metastasis, and 99 (48.5%) patients were without lymph node metastasis (**Table 1**).

#### Clinicopathological Factors Associated With Contralateral Occult Carcinoma

Among the 27 patients with occult lesions in the contralateral gland, 5 (18.5%) were men and 22 (81.5%) were women. Twenty-three (85.2%) patients were younger than 55 years and four (12.5%) patients were 55 years and older. The mean tumor size of the contralateral occult lesion was 2.00 ± 1.29, and the non-contralateral occult lesion was 1.14 ± 0.60. Six (22.2%) patients had a tumor size ≤ 1 cm, and 21 (77.7%) patients had a tumor size > 1 cm. Contralateral occult carcinoma presented with a significant association with tumor size and the presence of ETE, CLNM, and LLNM by univariate analysis (all $p < 0.05$). All of these factors were included in the multivariate analysis, which showed that a tumor size >1 cm (OR = 3.461, 95% CI = 1.333–8.984, $p = 0.011$) and the presence of ETE (OR = 11.481, 95% CI = 4.231–31.154, $p < 0.001$), CLNM (OR = 2.086, 95% CI = 1.246–3.495, $p = 0.005$), and LLNM (OR = 6.765, 95% CI = 1.877–24.380, $p = 0.003$) were independent predictors of contralateral occult carcinoma (**Table 1**).

### Meta-Analysis

After searching the databases, 118 studies were initially found, and 77 articles were determined to be non-overlapping articles. Eleven articles were excluded because of language, seven studies were excluded because they were case reports, and 43 studies were excluded because the title or abstract was not applicable. The remaining 16 articles were subjected to a full-text evaluation. However, patients in the five studies were non-unilateral PTC

**TABLE 1** | Associations between clinicopathological characteristics and contralateral occult carcinoma in PTC patients.

| Variables | Overall (N=204) | Contralateral occult N = 27 (13.2%) | Non-contralateral occult lesion N = 177 (86.8%) | P value | OR | 95% CI | P value |
|---|---|---|---|---|---|---|---|
| Sex | | | | | | | |
| Male | 47 (23.0) | 5 (10.6) | 42 (89.4) | 0.549 | | | |
| Female | 157 (77.0) | 22 (14.0) | 135 (86.0) | | | | |
| Age (Y) | 42.51 ± 10.42 | 42.85 ± 9.12 | 42.46 ± 10.63 | | | | |
| <55 | 172 (84.3) | 23 (13.4) | 149 (86.6) | 0.894 | | | |
| ≥55 | 32 (15.7) | 4 (12.5) | 28 (87.5) | | | | |
| Tumor size (cm) | 1.28 ± 0.77 | 2.00 ± 1.29 | 1.14 ± 0.60 | | | | |
| ≤1 | 94 (46.1) | 6 (6.4) | 88 (93.6) | 0.008 | 1 | | |
| >1 | 110 (53.9) | 21 (19.1) | 89 (80.9) | | 3.461 | 1.333–8.984 | 0.011 |
| ETE | | | | | | | |
| Absence | 183 (89.7) | 16 (8.7) | 167 (91.3) | <0.001 | 1 | | |
| Presence | 21 (10.3) | 11 (52.4) | 10 (47.6) | | 11.481 | 4.231–31.154 | <0.001 |
| LNM | | | | | | | |
| Without LNM | 99 (48.5) | 5 (5.1) | 94 (94.9) | 0.004 | 1 | | |
| CLNM | 65 (31.9) | 14 (21.5) | 51 (78.5) | | 2.086 | 1.246–3.495 | 0.005 |
| LLNM | 40 (19.6) | 8 (20.0) | 32 (80.0) | | 6.765 | 1.877–24.380 | 0.003 |

*PTC, papillary thyroid carcinoma; Y, year; ETE, extrathyroidal extension; LNM, lymph node metastasis; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; OR, odds ratio; 95% CI, 95% confidence interval.*

preoperatively, data could not be obtained in two studies, and one study had an overlapping population. A flowchart with details is displayed in **Figure 1**. Finally, a total of nine studies were included in the meta-analysis with our retrospective research data included. **Table 2** shows the baseline characteristics and quality scores of the nine studies included, which consisted of two prospective and seven retrospective studies with a total of 4347 patients enrolled. Eight studies were conducted in China and one in South Korea. All the studies enrolled patients who underwent TT or NT for the treatment of PTC confined to the unilateral lobe, without suspicious carcinoma lesion in the contralateral lobe by preoperative image examinations or FNA. Contralateral occult PTC was defined as a tumor lesion detected by pathology postoperatively in the contralateral lobe rather than detected by preoperative examinations. The prevalence of contralateral occult PTC in each study was available and ranged from 11.95% to 46.9% (median 16.7%). Among the 4,347 patients enrolled, contralateral occult PTC was reported in 1,150 patients, and the prevalence was 26.6%. According to Newcastle-Ottawa Scale (NOS), three studies were rewarded 6 stars, and six studies were rewarded 7 stars. The average award of the nine studies was 6.7 stars on a scale of 0 to 9. All studies were considered adequate for meta-analysis.

## Sex

There were 204 patients who met the criteria and were included in this retrospective study. Of these patients, 47 (23.0%) were men and 157 (77.0%) were women. There were 27 (13.2%) patients who had contralateral occult carcinoma and 177 (13.2%) did not; among the 27 patients with contralateral occult PTC, 5 (18.5%) were men, and 22 (81.5%) were women, sex had nothing to do with whether patients had contralateral occult PTC (**Table 1**).

Nine studies reported the relationship between the risk of contralateral occult PTC and sex, including our retrospective study. The pooled analysis revealed that sex was not associated with contralateral occult PTC (pooled OR = 0.98, 95% CI – 0.83–1.16, p = 0.80) (**Figure 2A**).

## Age

Age is a critical factor in outcomes for patients with well-differentiated thyroid cancer. Forty-five years was used as the cutoff value in staging before 2016. In four studies, the cutoff value for age was 45 years, and the pooled analysis revealed that 45 years as a cutoff value for age was not associated with the contralateral occult PTC (pooled OR = 0.93, 95% CI = 0.69–1.25, p = 0.33) (**Figure 2B**).

However, there is increasing evidence to suggest that regarded 45 years as the cutoff value for age may be too low. The newest guideline in the AJCC/UICC staging system changed the cutoff value for age from 45 years to 55 years in 2017. In our retrospective study, the patients' average age was 42.5 years, and the age range was 22 to 67 years. Briefly, 172 (84.3%) patients were younger than 55 years, and 32 (15.7%) patients were 55 years and older. In the 27 patients who had occult lesions in the contralateral gland, 23 patients (85.2%) were younger than 55 years, and 4 patients (12.5%) were 55 years or older. There were no differences on whether which patients had contralateral occult PTC between the two groups younger than 55 years and 55 years or older (**Table 1**). The results of the meta-analysis showed that the age cutoff value of 55 years was not associated with the contralateral occult PTC (pooled OR = 1.53, 95% CI = 0.87–2.68, p = 0.50) (**Figure 2C**).

## Tumor Size

In our retrospective study of 204 included PTC patients, the average tumor size was 1.28 cm, and the size range was 0.32 to 5.80 cm. In 93 (45.6%) patients, the tumor size was ≤ 1 cm, and for the other 111 (54.4%) patients, the tumor size was > 1 cm. However, in the contralateral occult PTC group, the mean tumor size of the lesion was 2.00 ± 1.29; and in the non-contralateral occult group, this value was 1.14 ± 0.60. In the contralateral occult PTC group, there were 6 (22.2%) patients whose tumor

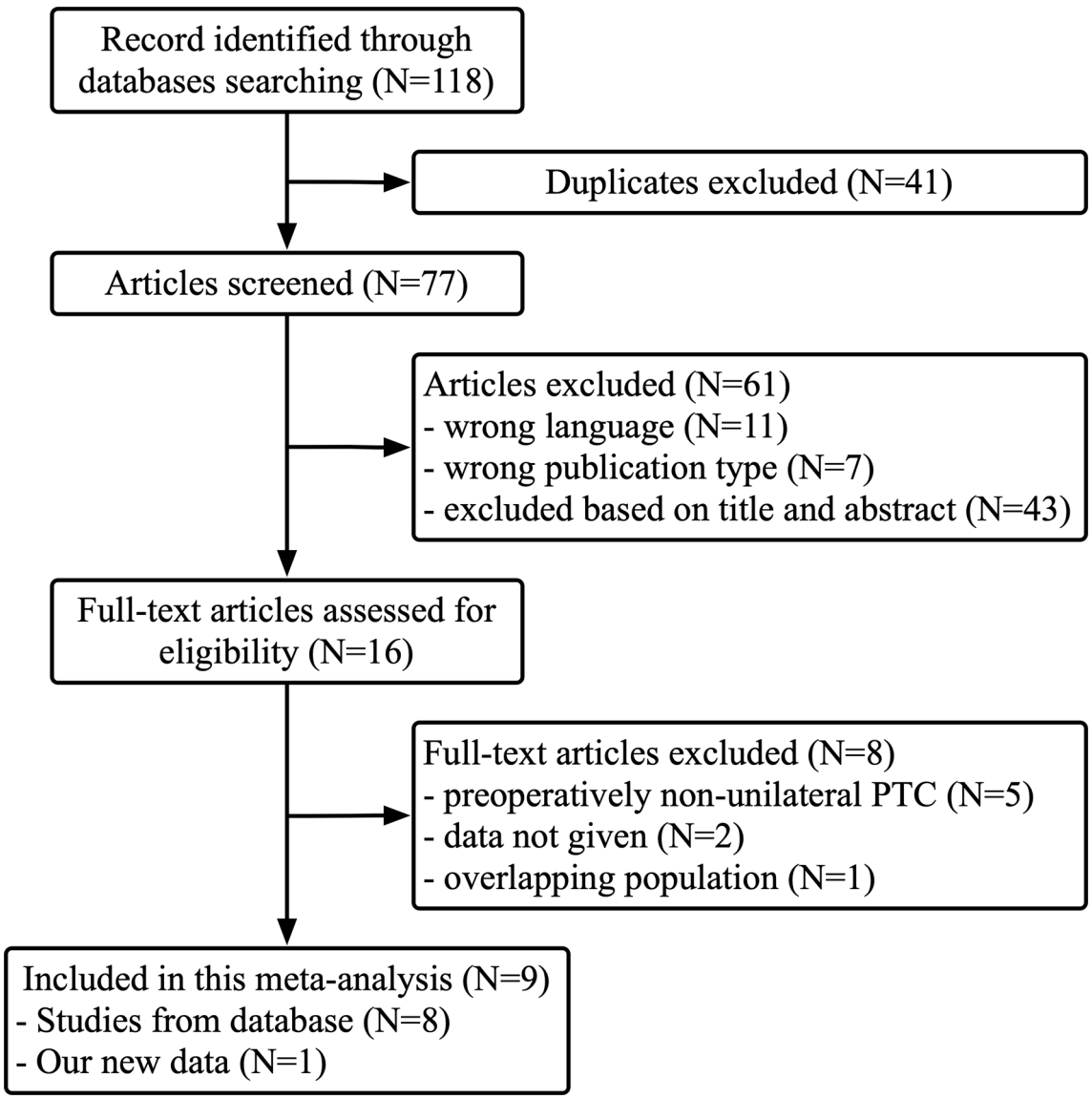


**FIGURE 1** | Flow chart of the study selection process.

size was ≤ 1 cm, and 21 (77.7%) patients whose tumor size was > 1 cm. The results of the univariate analysis showed that the presence of contralateral occult PTC had a significant association with tumor size ($p<0.05$). Also, the multivariable analysis showed that tumor size >1 cm (OR = 3.461, 95% CI = 1.333–8.984, p = 0.011) was an independent predictor of contralateral occult PTC (**Table 1**).

There were four studies (included our study) that estimated the effect of tumor size on contralateral occult PTC using the cutoff value of 1.0 cm. Findings from the pooled analysis suggested that the risk of contralateral occult PTC was significantly higher in patients with a tumor size > 1 cm than patients with a tumor size ≤ 1 cm (pooled OR = 2.16, 95% CI = 1.29–3.61, p = 0.003) (**Figure 2D**).

## Ipsilateral Multifocality

There were six studies that addressed the association between the risk of contralateral occult PTC and ipsilateral multifocality. Because of the low heterogeneity among the studies ($I^2$ = 45%, p = 0.11), a fixed-effects model was used to analyze the data. Compared with patients without ipsilateral multifocality, patients with ipsilateral multifocality had a higher prevalence of contralateral occult PTC (pooled OR = 5.62, 95% CI = 4.53–6.99, p < 0.00001) (**Figure 2E**).

## Extrathyroidal Extension (ETE)

In the 204 PTC patients included in this retrospective study, 21 (10.3%) patients had ETE and 183 patients (89.7%) did not. However, in the contralateral occult PTC group, there were 11

**TABLE 2** | Characteristics of the nine included studies.

| Author | Year | Country | Study Period | Study Design | Study Population | Case | Surgical Extent | Prevalence of contralateral occult PTC (%) | Quality assessment |
|---|---|---|---|---|---|---|---|---|---|
| Chen XH (12) | 2020 | China | 2014/1–2017/9 | Retrospective | PTC | 921 | TT/NT+CLND/CLND+LLND | 16.7 | 6 |
| Feng JW (16) | 2020 | China | 2011/1–2018/1 | Retrospective | PTC | 552 | TT+CLND/CLND+LLND | 16.1 | 7 |
| Gu JL (17) | 2020 | China | 2012/9–2014/9 | Retrospective | PTC | 300 | TT+CLND/CLND+LLND | 18.3 | 7 |
| Koo BS (18) | 2010 | Korea | 2005/3–2009/3 | Retrospective | PTMC | 132 | TT+CLND | 16.7 | 7 |
| Lv T (19) | 2018 | China | 2014/1–2016/12 | Retrospective | PTC | 1442 | TT+CLND | 46.9 | 7 |
| Wan HF (13) | 2015 | China | 2011/1–2013/12 | Prospective | PTMC | 89 | TT+ selective LND | 40.4 | 7 |
| Wang N (11) | 2020 | China | 2016/5–2018/6 | Retrospective | PTC | 586 | TT+ cervical LND | 11.95 | 6 |
| Zhou YL (20) | 2012 | China | 2010/11–2011/11 | Prospective | PTMC | 100 | TT+CLND | 20 | 6 |
| Our new data | 2021 | China | 2016/1–2021/1 | Retrospective | PTC | 204 | TT+CLND/CLND+LLND | 13.2 | 7 |

*PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma; TT, total thyroidectomy; NT, near-total thyroidectomy; CLND, central lymph node dissection; LLND, lateral lymph node dissection; LND, lymph node dissection.*

(40.7%) patients with ETE, the other 16 patients (59.3) did not. The results of the univariate analysis showed that the presence of contralateral occult PTC had a significant association with ETE ($p<0.05$). Also, the multivariable analysis showed that the presence of ETE (OR = 11.481, 95% CI = 4.231 (40.7%)31.154, $p < 0.001$) was an independent predictor of contralateral occult PTC (**Table 1**).

Seven studies analyzed the impact of ETE on contralateral occult PTC (including our new data). This pooled analysis suggested no significant association between ETE and contralateral occult PTC (pooled OR = 1.99, 95% CI = 0.63–6.26, p = 0.24) (**Figure 3A**).

## Capsular Invasion

Five studies addressed the association between the risk of contralateral occult PTC and capsular invasion. This risk factor showed low heterogeneity among the studies ($I^2 = 30\%$, p = 0.22). Results from the meta-analyses exhibited that the risk of capsular invasion was not associated with contralateral occult PTC (pooled OR = 1.20, 95% CI = 0.94–1.54, p = 0.15) (**Figure 3B**).

## *BRAF* Mutation

Six studies analyzed the impact of a *BRAF* mutation on contralateral occult PTC. The heterogeneity was 52% (p = 0.07). This pooled analysis suggested no significant association between a *BRAF* mutation and contralateral occult PTC (pooled OR = 1.58, 95% CI = 0.98–2.56, p = 0.06) (**Figure 3C**).

## Hashimoto Thyroiditis (HT)

An association between the risk of contralateral occult PTC and HT was investigated in four studies. Because no statistically significant heterogeneity was detected between the studies ($I^2 = 0\%$, p = 0.67), a fixed-effects model was applied to assess the data. The results from the meta-analyses showed that the risk of HT was not associated with contralateral occult PTC (pooled OR = 0.89, 95% CI = 0.61–1.30, p = 0.54) (**Figure 3D**).

## Contralateral Benign Nodule

Three studies estimated the effect of a contralateral benign nodule on contralateral occult PTC. Findings from the pooled analysis suggested that compared to patients without a contralateral benign nodule, patients with a contralateral benign nodule had a higher prevalence of contralateral occult PTC (pooled OR = 2.45, 95% CI = 1.20–5.03, p = 0.01) (**Figure 3E**).

## Lymph Node Metastasis

In our new data results, there were 65 (31.9%) patients who had central lymph node metastasis, 40 (19.6%) patients had lateral lymph node metastasis, and 99 (48.5%) patients without lymph node metastasis. However, in the contralateral occult PTC group, there were 14 (51.9%) patients with CLNM, 8 (29.6) patients with LLNM, and 5 (18.5%) patients without LNM. The results of the univariate analysis showed that the presence of contralateral occult PTC had a significant association with LNM ($p<0.05$). Also, the multivariable analysis showed that the presence of CLNM (OR = 2.086, 95% CI = 1.246–3.495, p=0.005) and LLNM (OR = 6.765, 95% CI = 1.877–24.380, p=0.003) were independent predictors of contralateral occult PTC (**Table 1**).

An association between the risk of contralateral occult PTC and CLNM was investigated in six studies. The heterogeneity was high (I2 = 88%, $p < 0.00001$), and the results from the meta-analyses showed that the risk of contralateral occult PTC was significantly higher in patients with CLNM than patients without CLNM (pooled OR = 2.80, 95% CI = 1.35–5.81, p = 0.006) (**Figure 4A**).

There were three studies that analyzed the impact of LLNM on contralateral occult PTC. The analysis suggested no significant association between LLNM and contralateral occult PTC (pooled OR = 3.99, 95% CI = 0.81–19.67, p = 0.09) (**Figure 4B**).

# DISCUSSION

Thyroid cancer has been the most rapidly increasing cancer over the past few decades in many countries. PTC comprises 90% of all thyroid malignancies and has an excellent prognosis with conventional therapies, such as surgery and radioactive iodine therapy. According to the latest ATA guidelines, TT is recommended for patients with a tumor > 4 cm, gross maximal ETE (T4), cervical lymph node metastasis, or distant metastasis. In addition, TL is endorsed as an initial surgical approach for low-risk, small- to medium-sized (T1-T2), N0 PTC in the absence of ETE (10). Considering that TT is associated with an increased risk of complications, such as vocal cord palsy and hypoparathyroidism (3, 21), TL may be sufficient for unilateral PTC with tumors < 4 cm and without ETE or clinical evidence of lymph node metastasis. There is no disagreement to performing TT for tumors detected

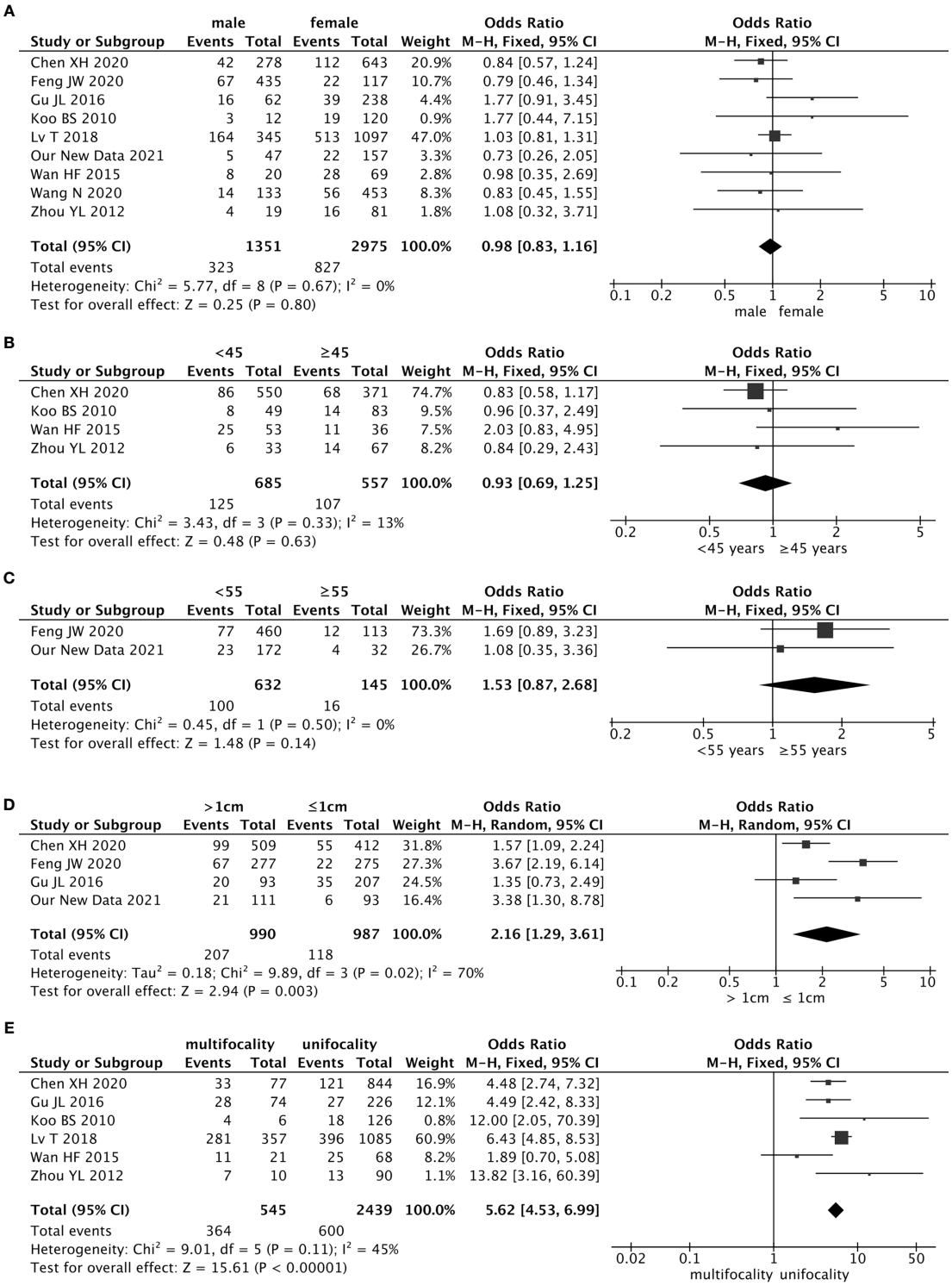


**FIGURE 2** | Forest plots of the association between contralateral occult PTC (papillary thyroid carcinoma) and all risk factors: **(A)** Sex was not associated with contralateral occult PTC (pooled OR = 0.98, 95% CI = 0.83–1.16, p = 0.80); **(B)** The risk of age (cut-off value was 55) was not associated with contralateral occult PTC (pooled OR = 1.53, 95% CI = 0.87–2.68, p = 0.14); **(C)** The risk of age (cut-off value was 45) was not associated with contralateral occult PTC (pooled OR = 0.93, 95% CI = 0.69–1.25, p = 0.63); **(D)** The risk of contralateral occult PTC was significantly higher in patients with a tumor > 1 cm than patients with a tumor ≤ 1 cm (pooled OR = 2.16, 95% CI = 1.1.29–3.61, p = 0.003); **(E)** Compared with patients without ipsilateral multifocality, patients with ipsilateral multifocality had a higher prevalence of contralateral occult PTC (pooled OR = 5.62, 95% CI = 4.53–6.99, p < 0.00001).

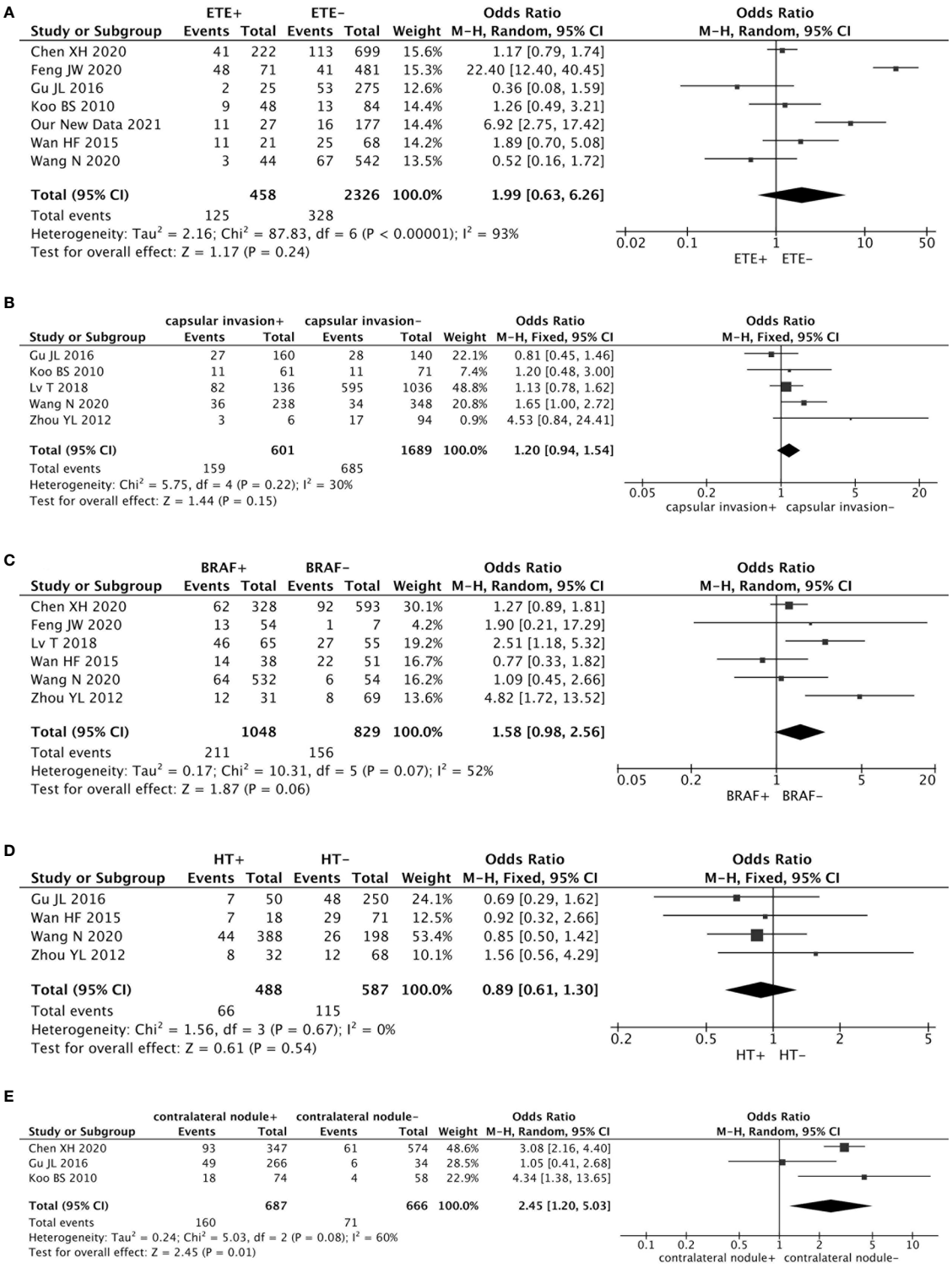


**FIGURE 3** | Forest plots of the association between contralateral occult PTC and all factors: **(A)** There was no significant association between ETE and contralateral occult PTC (pooled OR = 1.99, 95% CI = 0.63–6.26, p = 0.24); **(B)** The risk of capsular invasion was not associated with contralateral occult PTC (pooled OR = 1.20, 95% CI = 0.94–1.54, p = 0.15); **(C)** There was no significant association between a *BRAF* mutation and contralateral occult PTC (pooled OR = 1.58, 95% CI = 0.98–2.56, p = 0.06); **(D)** The risk of HT was not associated with contralateral occult PTC (pooled OR = 0.89, 95% CI = 0.61–1.30, p = 0.54); **(E)** Compared with patients without a contralateral benign nodule, patients with a contralateral benign nodule had a higher prevalence of contralateral occult PTC (pooled OR = 2.45, 95% CI = 1.20–5.03, p = 0.01).

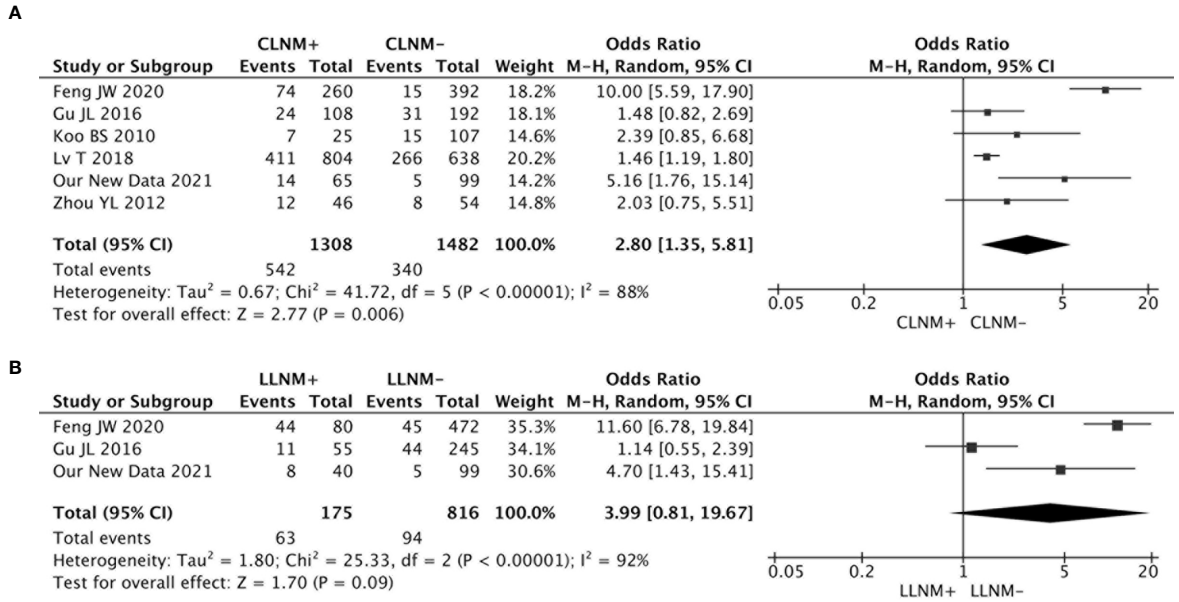


**FIGURE 4** | **(A)** The risk of contralateral occult PTC was significantly higher in patients with CLNM than patients without CLNM (pooled OR = 2.80, 95% CI = 1.35–5.81, p = 0.006); **(B)** There was no significant association between LLNM and contralateral occult PTC (pooled OR = 3.99, 95% CI = 0.81–19.67, p = 0.09).

preoperatively in bilateral lobes. However, when unilateral lobectomy is performed for patients with contralateral occult PTC, occult foci would lead to local recurrence and cervical lymph node metastasis and even re-operation, which is related to higher surgical risks compared with primary surgery (22, 23). Hence, we attempted to identify the risk factors for contralateral occult carcinoma to help select high-risk patients with occult carcinoma who would benefit from more extensive treatment.

Among patients with PTC, male patients have higher rates of ETE, regional lymph node, and distant metastasis, and mortality than female patients, regardless of age (24). Liu et al. reported that the male gender is an independent poor prognostic factor for all PTCs, and more aggressive treatment options should be considered for men (25). However, our pooled data showed that sex is not associated with the occurrence of contralateral occult PTC. Thus, there is no need to consider expanding the scope of lymph node dissection due to sex differences.

The biology of PTC is highly dependent on age, with young patients outperforming older patients in terms of survival (26). The previous guideline for thyroid cancer used 45 years as the cutoff age, and 55 years was the cutoff age used since 2017 (27). Thus, inclusion of a few of the literatures that used the previous guideline standard was inevitable. We set up two forest figures to suit two different cutoff values. Considering the effect of age on PTC's biological activity, older patients whose PTC might more malignant, contralateral occult PTC might more likely to happen. However, the results of meta-analysis showed that regardless of whether the age cutoff value is 45 or 55 years, it did not affect the occurrence of the contralateral occult PTC. However, there were only two studies (included in our new data) that regarded 55 years as the cutoff age, and the OR value was higher than the 45 years cutoff age. Therefore, after expanding the sample size, this difference may become more significant.

Tumor size is the first factor evaluated for the biological characteristics of PTC because it is easily measured by preoperative US. The relationship between the size of the tumor and the presence of contralateral occult carcinoma remains controversial. It was concluded that tumor size is an independent predictor of bilaterality in PTC patients (28, 29). This is consistent with our new results. However, Pitt et al. examined a cohort of 228 patients and reported a rate of contralateral PTC for patients with primary tumors ≥1, <1, and <0.5 cm (30%, 26%, and 27%, respectively; nonsignificant p-value for all) (30). Combining the results of our meta-analysis, we suspected that Pitt's results are limited by sample size. We suggest that researchers should perform a larger cohort study to clarify this problem.

Multifocality is a unique feature of PTC, and the rate of multifocality is reported to be 20% to 30% (31, 32). It was reported that increased tumor number is associated with higher rates of capsular invasion, ETE, and lymph node metastasis (33). A recent meta-analysis showed that multifocality in thyroid cancer increases the risk of disease recurrence (hazard ratio = 2.81; 95% CI = 1.07–7.36; p < 0.001) (34). What is more, Yoon et al. identified that multifocal tumors in the unilateral lobe have a high risk of bilateral carcinoma (9). Therefore, aggressive treatment, such as total thyroidectomy, central neck dissection, or postoperative radioactive iodine ablation, is suggested as the adequate treatment for multifocal PTCs. Our meta-analysis showed that patients with ipsilateral multifocal tumors have a 5.6-fold more contralateral occult PTC than patients with

single-tumor foci. Thus, we strongly recommend patients with multifocality to pay attention to the presence of contralateral occult PTC.

An ETE is defined as an extension of the primary tumor beyond the thyroid capsule into the perithyroidal soft tissues, strap muscles, and adjacent structures (35). ETE is a well-known and significant factor for poor prognosis. It was reported that patients with ETE have a lower 10-year survival rate (75.2%) and a lower 10-year disease-specific survival rate (84.2%) (36). Also, Feng et al. reported that ETE is more commonly found in bilateral PTC than unilateral PTC (20.2% *vs*. 11.4%, p = 0.016) (37). Therefore, it is conjectured that ETE would be a risk factor for contralateral concealed PTC, and our retrospective research also got the same results. However, this was not the case. The meta-analysis results showed that there was no association between ETE and contralateral occult PTC. We considered that the reason is that the ETE (+) patients' number was insufficient, ETE (+) patients accounted for about 7% to 37% of the total number in every study. This led to greater heterogeneity. What is more, the two studies with OR value <1 (from Gu et al. and Wang et al. respectively) had a percentage <10%. Less ETE (+) patients included, greater heterogeneity was important factor for the effect of ETE to contralateral occult PTC. Therefore, we suggest that researchers should perform a more perfect cohort study to get more credible conclusions.

In encapsulated thyroid neoplasms, the presence of capsular invasion is the most important criterion for separating benign neoplasms from malignancy. Currently, capsular invasion is defined in major guidelines as complete penetration of tumor capsules by neoplastic cells (38). Capsular invasion is not rare and has been reported from 9.9% to 26.8% of PTC (39). It was reported that capsular invasion is more common in patients with multifocal PTC and is related to tumor recurrence (33, 40). In our meta-analysis results, there is no connection between capsular invasion and contralateral occult PTC.

*BRAF* is a cytoplasmic protein kinase, and it is the main subtype of RAF kinase that could trigger tumorigenesis through the activation of the MAPK pathway. PTC patients with a *BRAF* mutation are associated with a higher risk of unfavorable clinicopathological characteristics (41). A study of 2,048 patients showed that a *BRAF* mutation is an independent risk factor for bilateral multifocal PTC (OR = 1.233, 95% CI = 1.063–1.431, p = 0.006) (42). However, we found no association between *BRAF* mutation and contralateral occult PTC. This may be because of the coexistent benign nodules in the contralateral lobe that could have affected the observed rate of contralateral occult carcinoma. The more useful reason may be the limited sample size; we considered that if there is an expanded sample size, the results would be reversed.

HT is the most common autoimmune thyroid disease. It causes the immune system to attack and destroy the thyroid gland and is the most common cause of primary hypothyroidism and nonendemic goiter. Liang et al. reported that PTC patients with HT have a higher rate of multifocality (p = 0.024) than patients without HT (42). This meta-analysis results showed no relation between HT and contralateral occult PTC.

Among the patients with unilateral PTC, a portion of them had contralateral thyroid nodules. A study of 1,442 patients reported that 667 (46.95%) patients with contralateral benign nodules were ultimately confirmed to be PTC (19). The therapeutic strategy for patients in this situation is controversial and challenging. Our data demonstrate that patients with contralateral benign nodules have increased contralateral occult PTC. This result may be because some small foci masked by a benign nodule in the contralateral lobe could lead to incorrect assessment during preoperative US or FNA. Therefore, we suggest that surgeons should evaluate the huge possibility of the presence of contralateral occult carcinoma in PTC patients with contralateral thyroid nodules and to deal with it more actively.

Multifocality might occur through the spread of an original tumor *via* intraglandular lymphatics. Cancer cells can cause metastasis to the contralateral gland through lymphatic dissemination, as well as lymph node metastasis. It is well established that PTC has a strong propensity for lymph node metastasis. Lymph node metastasis in PTC follows a predictable pattern. Most commonly, tumor cells metastasize to the central lymph node, followed by those of the lateral lymph node. Rarely, some patients develop LLNM in PTC without CLNM (43). It was reported that multifocality increases the risk of CLNM (44). However, the role of multifocality in LLNM remains a topic of debate (43, 45). Our results showed that patients with CLNM have more contralateral occult PTC but no significant relationship between LLNM and contralateral occult PTC. This might be because only three studies evaluated LLNM, and we considered that the result would be reversed by bringing in a large sample size research.

There are some limitations to this study. First, all of the studies were conducted in Asian countries. Second, most of the pooled studies were not prospective or randomized case-control trials. Third, the number of included studies was limited, which might have affected the results of our study, especially the risk factor analysis.

## CONCLUSION

The meta-analysis demonstrates the following risk factors for contralateral occult PTC: tumor size > 1 cm, ipsilateral multifocality, contralateral benign nodule, and CLNM. Sex, age, ETE, capsular invasion, *BRAF* mutation, HT, and LLNM do not affect contralateral occult PTC. Overall, although TT presents complications, the operation should be evaluated and implemented more actively when ≥ 1 risk factor is found in patients with PTC.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Science Research Ethics Committee of the First Hospital of China Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

FZ is the first author of this study. WT is the corresponding author supervising this work. FZ, BZ, and XW collected the clinical medical records. FZ and BZ conceived and designed the meta-analysis. BZ and XY performed the meta-analysis. FZ performed the statistical analyses of all the data and wrote the manuscript. XW and SW contributed material/analysis tools. FZ and BZ collected reference and managed the data. FZ and WT designed the study. All authors contributed to the article and approved the submitted version.

## FUNDING

This study was supported by The Research Fund for Public Welfare, National Health and Family Planning Commission of China (grant 201402005). The funder had no role in study design, data collection or analysis, or in the presentation or publication of the results.

## REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2020. *CA Cancer J Clin* (2020) 70(1):7–30. doi: 10.3322/caac.21590
2. Powers AE, Marcadis AR, Lee M, Morris LGT, Marti JL. Changes in Trends in Thyroid Cancer Incidence in the United States, 1992 to 2016. *JAMA* (2019) 322(24):2440–1. doi: 10.1001/jama.2019.18528
3. Hauch A, Al-Qurayshi Z, Randolph G, Kandil E. Total Thyroidectomy Is Associated With Increased Risk of Complications for Low- and High-Volume Surgeons. *Ann Surg Oncol* (2014) 21(12):3844–52. doi: 10.1245/s10434-014-3846-8
4. Yang L, Shen W, Sakamoto N. Population-Based Study Evaluating and Predicting the Probability of Death Resulting From Thyroid Cancer and Other Causes Among Patients With Thyroid Cancer. *J Clin Oncol* (2013) 31 (4):468–74. doi: 10.1200/JCO.2012.42.4457
5. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. *JAMA* (2017) 317 (13):1338–48. doi: 10.1001/jama.2017.2719
6. Chen HY, Liu WY, Zhu H, Jiang DW, Wang DH, Chen Y, et al. Diagnostic Value of Contrast-Enhanced Ultrasound in Papillary Thyroid Microcarcinoma. *Exp Ther Med* (2016) 11(5):1555–62. doi: 10.3892/etm.2016.3094
7. Kuo SF, Lin SF, Chao TC, Hsueh C, Lin KJ, Lin JD. Prognosis of Multifocal Papillary Thyroid Carcinoma. *Int J Endocrinol* (2013) 2013:809382. doi: 10.1155/2013/809382
8. Ng SC, Kuo SF, Chen ST, Hsueh C, Huang BY, Lin JD. Therapeutic Outcomes of Patients With Multifocal Papillary Thyroid Microcarcinomas and Larger Tumors. *Int J Endocrinol* (2017) 2017:4208178. doi: 10.1155/2017/4208178
9. So YK, Kim MW, Son YI. Multifocality and Bilaterality of Papillary Thyroid Microcarcinoma. *Clin Exp Otorhinolaryngol* (2015) 8(2):174–8. doi: 10.3342/ceo.2015.8.2.174
10. 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* (2016) 26(1):1–133. doi: 10.1089/thy.2015.0020
11. Wang N, Qian LX. Predictive Factors for Occult Bilateral Papillary Thyroid Carcinoma. *Acad Radiol* (2021) 28(3):328–32. doi: 10.1016/j.acra.2020.01.023
12. Chen X, Zhong Z, Song M, Yuan J, Huang Z, Du J, et al. Predictive Factors of Contralateral Occult Carcinoma in Patients With Papillary Thyroid Carcinoma: A Retrospective Study. *Gland Surg* (2020) 9(4):872–8. doi: 10.21037/gs-19-157
13. Wan HF, Zhang B, Yan DG, Xu ZG. The BRAFT1799A Mutation Is Not Associated With Occult Contralateral Carcinoma in Patients With Unilateral Papillary Thyroid Microcarcinoma. *Asian Pac J Cancer Prev* (2015) 16 (7):2947–51. doi: 10.7314/APJCP.2015.16.7.2947
14. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Open Med* (2009) 3(3):e123–30.
15. Stang A. Critical Evaluation of the Newcastle-Ottawa Scale for the Assessment of the Quality of Nonrandomized Studies in Meta-Analyses. *Eur J Epidemiol* (2010) 25(9):603–5. doi: 10.1007/s10654-010-9491-z
16. Feng JW, Ye J, Wu WX, Pan H, Qin AC, Jiang Y, et al. Management of Clinically Solitary Papillary Thyroid Carcinoma Patients According to Risk-Scoring Model for Contralateral Occult Carcinoma. *Front Endocrinol (Lausanne)* (2020) 11:553577. doi: 10.3389/fendo.2020.553577
17. Gu JL, Nie XL, Wang WD, Xiang YF, Jiang L, Shang JB. Multifocality of the Primary Tumor Is a Predictive Factor for Contralateral Occult Carcinoma in Patients With Unilateral Papillary Thyroid Carcinoma. *Int J Clin Exp Patho* (2016) 9(11):11972–7. doi: 10.1089/thy.2015.0315
18. Koo BS, Lim HS, Lim YC, Yoon YH, Kim YM, Park YH, et al. Occult Contralateral Carcinoma in Patients With Unilateral Papillary Thyroid Microcarcinoma. *Ann Surg Oncol* (2010) 17(4):1101–5. doi: 10.1245/s10434-009-0906-6
19. Lv T, Zhu C, Di Z. Risk Factors Stratifying Malignancy of Nodules in Contralateral Thyroid Lobe in Patients With Pre-Operative Ultrasound Indicated Unilateral Papillary Thyroid Carcinoma: A Retrospective Analysis From Single Centre. *Clin Endocrinol (Oxf)* (2018) 88(2):279–84. doi: 10.1111/cen.13506
20. Zhou YL, Zhang W, Gao EL, Dai XX, Yang H, Zhang XH, et al. Preoperative BRAF Mutation Is Predictive of Occult Contralateral Carcinoma in Patients With Unilateral Papillary Thyroid Microcarcinoma. *Asian Pac J Cancer Prev* (2012) 13(4):1267–72. doi: 10.7314/APJCP.2012.13.4.1267
21. Vaiman M, Nagibin A, Olevson J. Complications in Primary and Completed Thyroidectomy. *Surg Today* (2010) 40(2):114–8. doi: 10.1007/s00595-008-4027-9
22. Raffaelli M, De Crea C, Sessa L, Giustacchini P, Revelli L, Bellantone C, et al. Prospective Evaluation of Total Thyroidectomy Versus Ipsilateral Versus Bilateral Central Neck Dissection in Patients With Clinically Node-Negative Papillary Thyroid Carcinoma. *Surgery* (2012) 152(6):957–64. doi: 10.1016/j.surg.2012.08.053
23. So YK, Seo MY, Son YI. Prophylactic Central Lymph Node Dissection for Clinically Node-Negative Papillary Thyroid Microcarcinoma: Influence on Serum Thyroglobulin Level, Recurrence Rate, and Postoperative Complications. *Surgery* (2012) 151(2):192–8. doi: 10.1016/j.surg.2011.02.004
24. Nilubol N, Kebebew E. Should Small Papillary Thyroid Cancer be Observed? A population-based study. *Cancer* (2015) 121(7):1017–24. doi: 10.1002/cncr.29123
25. Liu C, Chen T, Zeng W, Wang S, Xiong Y, Liu Z, et al. Reevaluating the Prognostic Significance of Male Gender for Papillary Thyroid Carcinoma and

Microcarcinoma: A SEER Database Analysis. *Sci Rep* (2017) 7(1):11412. doi: 10.1038/s41598-017-11788-8
26. Haymart MR. Understanding the Relationship Between Age and Thyroid Cancer. *Oncologist* (2009) 14(3):216–21. doi: 10.1634/theoncologist.2008-0194
27. 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* (2016) 26(3):373–80. doi: 10.1089/thy.2015.0315
28. Lee KJ, Cho YJ, Kim JG, Lee DH. How Many Contralateral Papillary Thyroid Carcinomas can be Missed? *World J Surg* (2013) 37(4):780–5. doi: 10.1007/s00268-013-1913-0
29. Zhou YL, Gao EL, Zhang W, Yang H, Guo GL, Zhang XH, et al. Factors Predictive of Papillary Thyroid Micro-Carcinoma With Bilateral Involvement and Central Lymph Node Metastasis: A Retrospective Study. *World J Surg Oncol* (2012) 10:67. doi: 10.1186/1477-7819-10-67
30. Pitt SC, Sippel RS, Chen H. Contralateral Papillary Thyroid Cancer: Does Size Matter? *Am J Surg* (2009) 197(3):342–7. doi: 10.1016/j.amjsurg.2008.09.011
31. Hay ID, Hutchinson ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS, et al. Papillary Thyroid Microcarcinoma: A Study of 900 Cases Observed in a 60-Year Period. *Surgery* (2008) 144(6):980–7; discussion 7-8. doi: 10.1016/j.surg.2008.08.035
32. Zhang L, Wei WJ, Ji QH, Zhu YX, Wang ZY, Wang Y, et al. Risk Factors for Neck Nodal Metastasis in Papillary Thyroid Microcarcinoma: A Study of 1066 Patients. *J Clin Endocrinol Metab* (2012) 97(4):1250–7. doi: 10.1210/jc.2011-1546
33. Tam AA, Ozdemir D, Cuhaci N, Baser H, Aydin C, Yazgan AK, et al. Association of Multifocality, Tumor Number, and Total Tumor Diameter With Clinicopathological Features in Papillary Thyroid Cancer. *Endocrine* (2016) 53(3):774–83. doi: 10.1007/s12020-016-0955-0
34. Joseph KR, Edirimanne S, Eslick GD. Multifocality as a Prognostic Factor in Thyroid Cancer: A Meta-Analysis. *Int J Surg* (2018) 50:121–5. doi: 10.1016/j.ijsu.2017.12.035
35. Ortiz S, Rodriguez JM, Soria T, Perez-Flores D, Pinero A, Moreno J, et al. Extrathyroid Spread in Papillary Carcinoma of the Thyroid: Clinicopathological and Prognostic Study. *Otolaryngol Head Neck Surg* (2001) 124(3):261–5. doi: 10.1067/mhn.2001.113141
36. Jin BJ, Kim MK, Ji YB, Song CM, Park JH, Tae K. Characteristics and Significance of Minimal and Maximal Extrathyroidal Extension in Papillary Thyroid Carcinoma. *Oral Oncol* (2015) 51(8):759–63. doi: 10.1016/j.oraloncology.2015.05.010
37. Feng JW, Qu Z, Qin AC, Pan H, Ye J, Jiang Y. Significance of Multifocality in Papillary Thyroid Carcinoma. *Eur J Surg Oncol* (2020) 46(10 Pt A):1820–8. doi: 10.1016/j.ejso.2020.06.015
38. Haugen BR, Sawka AM, Alexander EK, Bible KC, Caturegli P, Doherty GM, et al. American Thyroid Association Guidelines on the Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force Review and Recommendation on the Proposed Renaming of Encapsulated Follicular Variant Papillary Thyroid Carcinoma Without Invasion to Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features. *Thyroid* (2017) 27(4):481–3. doi: 10.1089/thy.2016.0628
39. Li M, Zhu XY, Lv J, Lu K, Shen MP, Xu ZL, et al. Risk Factors for Predicting Central Lymph Node Metastasis in Papillary Thyroid Microcarcinoma (CN0): A Study of 273 Resections. *Eur Rev Med Pharmacol Sci* (2017) 21(17):3801–7.
40. Giordano D, Gradoni P, Oretti G, Molina E, Ferri T. Treatment and Prognostic Factors of Papillary Thyroid Microcarcinoma. *Clin Otolaryngol* (2010) 35(2):118–24. doi: 10.1111/j.1749-4486.2010.02085.x
41. Zhang Q, Liu SZ, Zhang Q, Guan YX, Chen QJ, Zhu QY. Meta-Analyses of Association Between BRAF(V600E) Mutation and Clinicopathological Features of Papillary Thyroid Carcinoma. *Cell Physiol Biochem* (2016) 38(2):763–76. doi: 10.1159/000443032
42. Yan C, Huang M, Li X, Wang T, Ling R. Relationship Between BRAF V600E and Clinical Features in Papillary Thyroid Carcinoma. *Endocr Connect* (2019) 8(7):988–96. doi: 10.1530/EC-19-0246
43. Liang J, Zeng W, Fang F, Yu T, Zhao Y, Fan X, et al. Clinical Analysis of Hashimoto Thyroiditis Coexistent With Papillary Thyroid Cancer in 1392 Patients. *Acta Otorhinolaryngol Ital* (2017) 37(5):393–400. doi: 10.14639/0392-100X-1709
44. Al Afif A, Williams BA, Rigby MH, Bullock MJ, Taylor SM, Trites J, et al. Multifocal Papillary Thyroid Cancer Increases the Risk of Central Lymph Node Metastasis. *Thyroid* (2015) 25(9):1008–12. doi: 10.1089/thy.2015.0130
45. Hu D, Zhou J, He W, Peng J, Cao Y, Ren H, et al. Risk Factors of Lateral Lymph Node Metastasis in cN0 Papillary Thyroid Carcinoma. *World J Surg Oncol* (2018) 16(1):30. doi: 10.1186/s12957-018-1336-3

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 22 July 2021
doi: 10.3389/fendo.2021.653184

# Clinical Relevance and Management of Recurrent Laryngeal Nerve Inlet Zone Lymph Nodes Metastasis in Papillary Thyroid Cancer

*Guibin Zheng[1], Guochang Wu[1], Haiqing Sun[1], Chi Ma[1], Yawen Guo[1], Dongmin Wei[2], Wenbin Yu[3]*, Haitao Zheng[1]* and Xicheng Song[4]**

*[1] Department of Thyroid Surgery, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, China, [2] Department of Otorhinolaryngology, Qilu Hospital of Shandong University, NHC Key Laboratory of Otorhinolaryngology (Shandong University), Jinan, China, [3] Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Head and Neck Surgery, Peking University Cancer Hospital & Institute, Beijing, China, [4] Department of Otolaryngology-Head and Neck Surgery, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, China*

**Background:** Recurrent nodal disease often occurs in recurrent laryngeal nerve inlet zone (RLNIZ), leading to difficult surgical management.

**Methods:** Medical records of 947 patients with PTC and 33 patients with recurrent PTC were retrospectively reviewed. Totally 169 sides of RLNIZ dissection in 152 patients (17 cases were bilateral and 135 cases were unilateral) with primary surgery and 4 patients with structural recurrent disease were included for the analysis.

**Results:** The rate of lymph node metastasis in RLNIZ was 31.3% (47/150). The incidence of transient hypoparathyroidism was 5.9% and no RLN injury and permanent hypoparathyroidism occurred. RLNIZ lymph nodes metastasis (LNM) was significantly associated with age <45 years, larger tumor size, number of CNLNM, and lateral node metastasis. CNLNM and lateral node metastasis were independent risk factors for RLNIZ LNM. Recurrent nodal disease in RLNIZ was identified in four of 33 patients and permanent recurrent laryngeal nerve (RLN) injury was observed in one of four patients.

**Conclusion:** Lymph nodes in RLNIZ are usually involved in patients with heavy tumor burden and can be removed safely at initial surgery. Once central or lateral LNM was confirmed preoperatively or intraoperatively, RLNIZ lymph node dissection should be carefully performed to reduce the rate of structural recurrence in the central compartment.

**Keywords: papillary thyroid cancer, recurrent laryngeal nerve inlet zone, lymph nodes metastasis, recurrent nodal disease, neck dissection**

OPEN ACCESS

***Edited by:***
*Christoph Reiners, University Hospital Würzburg, Germany*

***Reviewed by:***
*Erivelto Martinho Volpi, Centro de referencia no ensino do diagnóstico por imagem (CETRUS), Brazil*
*Leonardo Rossi, University of Pisa, Italy*

***Correspondence:**
*Xicheng Song*
*songxicheng@126.com*
*Haitao Zheng*
*zhenghaitao1972@126.com*
*Wenbin Yu*
*yuwenbin429@qq.com*

***Specialty section:***
*This article was submitted to Thyroid Endocrinology, a section of the journal Frontiers in Endocrinology*

***Received:*** *16 May 2021*
***Accepted:*** *29 June 2021*
***Published:*** *22 July 2021*

***Citation:***
*Zheng G, Wu G, Sun H, Ma C, Guo Y, Wei D, Yu W, Zheng H and Song X (2021) Clinical Relevance and Management of Recurrent Laryngeal Nerve Inlet Zone Lymph Nodes Metastasis in Papillary Thyroid Cancer. Front. Endocrinol. 12:653184. doi: 10.3389/fendo.2021.653184*

## INTRODUCTION

Papillary thyroid cancer (PTC) is an indolent malignant tumor with low mortality. Central lymph node metastasis has been reported in approximately 31.5–50% of patients with PTC at initial surgery (1–4). In spite of low mortality, 3–7.9% of patients have loco-regional recurrence within 5 years after initial surgery (5–9). Of these patients, structural recurrence in the central compartment accounts for 20–55.6% of all loco-regional recurrences (4, 7, 9–11). This proportion of early nodal recurrence reflects the inadequacy of initial surgical management (12, 13). Surgical reintervention for central compartment recurrences especially for RLN inlet region is more challenging and may substantially increase the risk of recurrent laryngeal nerve (RLN) injury as well as permanent hypoparathyroidism. The latter results from tissue scarring, and disruption of normal anatomy may lead to an overall reduced quality of life for the survivor (11).

Clayman et al. (14) reported precise locations of recurrent lymph nodes within the central compartment and that 22.4% (47/210) of patients with recurrent disease had metastatic nodal disease in the RLN inlet. Such patients had high risk for treatment. However, this study did not have a clear definition of region for metastatic nodal disease in RLN inlet. The RLN inlet is closely surrounded by the thyroid gland, esophagus, trachea and cricoid cartilage, which form a latent space adjacent to RLN inlet, named RLN inlet zone (RLNIZ). RLNIZ belongs to paratracheal subregion of central compartment and lacks adipose tissue. Lymph nodes in RLNIZ are small and uncommon. Although lymph nodes in RLNIZ are part of paratracheal lymph nodes, these lymph nodes may be easily omitted during surgery or may be intentionally overlooked for concerns of RLN and parathyroid gland injury. Detailed investigation of lymph node metastasis in RLNIZ would provide crucial information for optimizing the initial surgical intervention. However, there is limited evidence focused on metastatic nodal disease in RLNIZ in patients with PTC.

This study aims to explore the prevalence and characteristics of metastatic lymph nodes in RLNIZ in patients with PTC at primary surgery and to determine the surgical management of patients with structural recurrence at RLNIZ.

## METHODS AND STUDY PATIENTS

### Patients

We retrospectively reviewed the medical records of 947 patients with PTC and 33 patients with recurrent PTC between July 1, 2017 and June 30, 2018 in the Department of Thyroid Surgery and Department of Otorhinolaryngology-Head & Neck Surgery at the Affiliated Yantai Yuhuangding Hospital of Qingdao University. Recurrence was determined by fine-needle aspiration biopsy in all 33 patients with previous history of surgery for PTC. Structural recurrent disease in RLNIZ was evaluated by CT scan preoperatively and confirmed by histopathological examination postoperatively. Ipsilateral central neck dissection (CND) was performed routinely in all patients with PTC at primary surgery. Patients with pathological examination of tissues in RLNIZ removed separately were included in the study. This cohort is comprised of 152 patients who underwent primary surgery for PTC and four patients with structural recurrent disease in RLNIZ. The study protocol was approved by the Committee of Ethics in Research of our institution.

### Anatomy of RLNIZ

RLNIZ refers to the convergence area of important anatomical structures related to the thyroid surgery including RLN, Berry ligament, branches of inferior thyroid artery that enter the thyroid lobe near the RLN inlet and superior parathyroid gland (SPG). In this region, Berry ligament firmly anchors the thyroid gland to the trachea and then forms a latent space lacking adipose tissue. The boundaries of RLNIZ are: cricoid cartilage, located superiorly; the upper part of trachea, located medially; and the lateral side of thyroid gland, located laterally. There is no clear inferior boundary of RLNIZ due to the variability of the horizontal segment of inferior thyroid artery traversing RLN. Therefore, based on the anatomical structures and the difficulty of surgical intervention, we defined RLNIZ as a 1-cm radius space around RLN inlet for the purpose of this study (**Figure 1**).

### Surgery Strategies and Removal of RLNIZ Lymph Nodes

The surgery strategies for PTC were selected according to the guidelines in China as follows: Unilateral thyroidectomy plus isthmectomy was performed for unilateral PTC. Total thyroidectomy was performed for bilateral PTC or unilateral PTC with tumor size over 4 cm. Prophylactic central neck dissection (CND) was routinely performed on the tumor side. Lateral neck dissection was performed when metastatic lymph nodes on the lateral neck were confirmed preoperatively by fine needle aspiration biopsy and wash-out thyroglobulin (Tg) or by intraoperative frozen biopsy.

CND was performed after thyroidectomy. Removal of RLNIZ lymph nodes was performed under a direct vision of RLN as the final step of CND. RLNIZ was meticulously dissected and explored during primary surgery. Any tissue identified was deliberately removed, labeled as the RLNIZ lymph nodes and sent for paraffin pathology examination separately. In patients with recurrence disease, RLNIZ dissection was only performed with the confirmation of structural recurrence in RLNIZ by preoperative ultrasonography and/or enhanced CT scan in order to decrease the risk of RLN injury. All the surgeries were performed by high-volume surgeons.

### Data Collection and Statistical Analysis

As RLNIZ dissection was performed bilaterally in some patients with bilateral PTC, the clinicopathological data were collected for

**Abbreviations:** CND, central neck dissection; CNLNM, central neck lymph nodes metastasis; CNs, carbon nanoparticles; CT, computer tomography; LNM, lymph nodes metastasis; PTC, papillary thyroid cancer; RAI, adjuvant radioactive iodine; RLN, recurrent laryngeal nerve; RLNIZ, recurrent laryngeal nerve inlet zone; SPG, superior parathyroid gland; Tg, thyroglobulin.

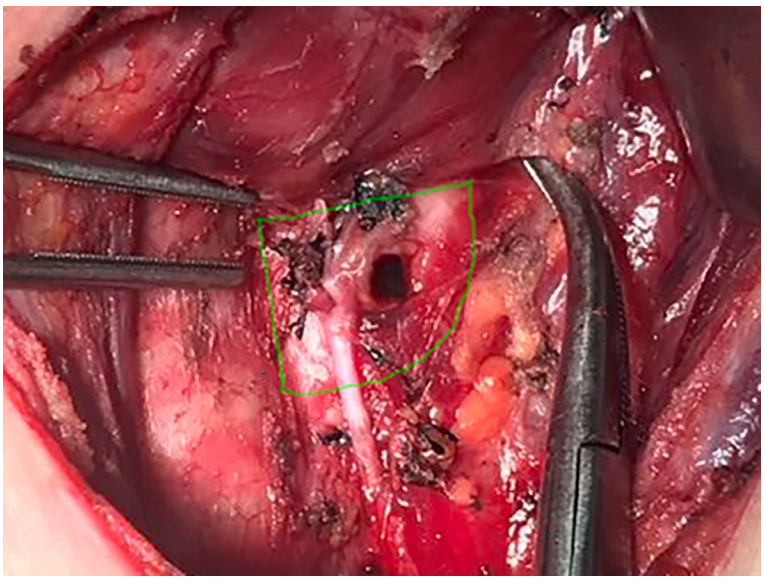

**FIGURE 1** | The region of RLNIZ. Green line showed the region of RLNIZ needed to be dissected during surgery.

analysis based on the sides of RLNIZ removal rather than the number of patients. SPSS v. 20.0 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. Categorical variables were tested with Chi-square test or Kruskal–Wallis test. Continuous variables were analyzed using the Student's t-test or Mann–Whitney U test. Characteristics found to be significantly different between groups in the univariate analysis were included in the multivariate logistic regression analysis. Differences were considered significant when $P$ <0.05.

# RESULTS

## Characteristics of Patients Who Underwent Primary Surgery

Unilateral RLNIZ dissection was performed in 135 patients, and bilateral RLNIZ dissection was performed in 17 patients with bilateral PTC. Thus, totally 169 sides of RLNIZ dissection were performed in 152 patients. Of these patients, 83 (54.6%) were found to have central neck lymph node metastasis (CNLNM). Of 169 sides that had RLNIZ removed, thirteen (7.7%) were merely fibrous adipose tissue, nine (5.3%) had thyroid tissue, and three (1.8%) were confirmed as parathyroid glands by histopathology. Lymph nodes in RLNIZ were harvested in 150 sides of 136 patients (**Table 1**). Metastatic disease to RLNIZ was observed in 47 out of 150 sides (31.3%). The median number and size of lymph nodes in RINIZ was 1 (range: 1–4) and 0.25 cm (range: 0.1–0.6 cm), respectively. Of the 150 sides of RLNIZ, eight (5.3%) had only RLNIZ lymph node metastasis in the central compartment.

Univariate analysis was performed between the group with (n = 47) and without (n = 103) RLNIZ lymph node metastasis.

**TABLE 1** | Clinical characteristics of patients with primary surgery for PTC who had lymph nodes in RLNIZ.

| Characteristics | RLNIZ+ (%) [n = 47]§ | RLNIZ– (%) [n = 103] § | *P-value* |
|---|---|---|---|
| Sex | | | 0.325* |
| Female | 31 (66.0) | 76(73.8) | |
| Male | 16 (34.0) | 27(26.2) | |
| Age | | | <0.001* |
| <45 years | 31 (66.0) | 31 (30.1) | |
| ≥45 years | 16 (34.0) | 7 2(69.9) | |
| Tumor location | | | 0.994 |
| Upper 1/3 | 7 (14.9) | 15 (14.6) | |
| Middle 1/3 | 33 (70.2) | 72 (69.9) | |
| Lower 1/3 | 7 (14.9) | 16 (15.5) | |
| Thyroiditis | | | 0.611* |
| Present | 14 (29.8) | 35 (34.0) | |
| Absent | 33 (70.2) | 68 (66.9) | |
| Capsular invasion | 32 (68.1) | 58 (56.3) | 0.172* |
| Tumor size(cm) | 1.2 ± 0.8 | 0.8 ± 0.5 | 0.005† |
| Multifocality | | | 0.628* |
| Yes | 8 (17.0) | 21 (25.6) | |
| No | 39 (83.0) | 82 (79.6) | |
| $BRAF^{V600E}$ gene | | | 0.769¶ |
| Mutant | 24 (51.1) | 59 (57.3) | |
| Wild type | 13 (27.7) | 24 (23.3) | |
| Undetected | 10 (21.3) | 20 (19.4) | |
| No. of central nodes removed | 11.5 ± 5.2 | 10.8 ± 4.5 | 0.355† |
| No. of CNLNM | 6.1 ± 4.7 | 1.1 ± 2.1 | <0.001† |
| Lateral nodes metastasis | | | <0.001* |
| Present | 18 (38.3) | 3 (2.9) | |
| Absent | 29 (61.7) | 100 (97.1) | |
| No. of lateral nodes removed | 28.8 ± 9.6 | 23.7 ± 12.9 | 0.417† |
| No. of LNLNM | 6.1 ± 4.2 | 1.6 ± 1.2 | 0.017‡ |

**Chi-square test. †Student's t-test. ‡Mann–Whitney U test. ¶Kruskal–Wallis test. §Number of the RLNIZ sides. + positive for metastatic disease; – negative for metastatic disease. RLNIZ, recurrent laryngeal nerve inlet zone; CNLNM, central neck lymph nodes metastasis; NLNM, lateral neck lymph node metastasis.*

Metastatic disease to RINIZ was associated with age<45 years (66.0 *vs*. 30.1%, $P < 0.001$, larger tumor size (1.2 ± 0.8 *vs*. 0.8 ± 0.5, $P = 0.005$), number of CNLNM (6.1 ± 4.7 *vs*. 1.1 ± 2.1, $P < 0.001$) and lateral node metastasis (38.3 *vs*. 2.9%, $P < 0.001$) as shown in **Table 1**. There were no significant effects of sex, tumor location, thyroiditis, capsular invasion, and $BRAF^{V600E}$ mutation. Multivariate analyses showed a statistically significant difference in age<45 years ($P = 0.014$), number of CNLNM ($P < 0.001$), and lateral node metastasis ($P = 0.019$) as shown in **Table 2**.

Of these 152 patients, no RLN injury or permanent hypoparathyroidism was observed. Temporary hypoparathyroidism occurred in nine out of 152 patients (5.9%). Nine patients with total thyroidectomy and lateral neck dissection were treated with adjuvant radioactive iodine (RAI) postoperatively. The median follow-up time was 16 months (range, 12–28), no recurrent disease was found by US or serum Tg.

## Characteristics of Patients With Recurrent Disease in RLNIZ

During this study period, recurrent disease in RLNIZ was found in four of 33 patients (12.1%) as shown in **Table 3** and **Figure 2**. The information of the primary tumors of those four patients was unknown because their initial surgery for PTC was performed in other institutions. Recurrent disease in RLNIZ was examined by enhanced CT scan and confirmed by histopathological examination after surgery. In case 1 (**Figure 2A**), recurrent disease in RLNIZ was the major finding by preoperative ultrasonography. Permanent RLN injury occurred in one of four patients (25%). No temporary RLN paralysis or hypocalcemia was noted. RAI was given to those four patients; none of them showed any evidence of recurrent disease during the follow-up period.

**TABLE 2** | Multivariable analysis of RLNIZ lymph node metastasis in patients with primary surgery for PTC.

| Characteristics | OR | 95% CI | *P* |
|---|---|---|---|
| Age<45 years | 0.274 | 0.097–0.771 | 0.014 |
| Tumor size | 1.343 | 0.613–2.944 | 0.462 |
| No. of CNLNM | 1.674 | 1.353–2.072 | <0.001 |
| Lateral nodes metastasis | 7.122 | 1.383–36.668 | 0.019 |

*RLNIZ, recurrent laryngeal nerve inlet zone. OR, odds ratio; CI, confidence interval. CNLNM, central neck lymph nodes metastasis.*

# DISCUSSION

RLNIZ, a convergence zone of several important anatomical structures, is a region often involved with recurrent nodal disease of PTC that is difficult to manage because of the dense adhesion (14, 15). To the best of our knowledge, RLNIZ is defined based on a surgical experience, and the standardized definition remains lacking. However, surgeons should pay more attention to this region of primary surgery to reduce the risk of RLN injury, as this region may have surgeons perform subtotal thyroidectomy or unintentionally neglect small lymph nodes. In this study, we referred to RLNIZ as a 1-cm radius space around RLN inlet for several reasons. First, there is no clear inferior boundary of RLNIZ due to the variability of the horizontal segment of inferior thyroid artery traversing RLN; second, there are constant small vessels that enter the gland within 1 cm region near the RLN inlet, and bleeding usually occurs in this region when dissecting RLN and excising lymph nodes; and third, small gland and lymph nodes are usually left in the 1-cm radius space due to concern for RLN injury. Given that recurrent nodal disease in RLNIZ is not rare (14), more attention should be paid to the dissection of lymph nodes in RLNIZ for primary surgery.

Our results found that lymph nodes in RLNIZ were detected in 89.5% (136/152) of patients with PTC at initial surgery. Of the 150 RLNIZ sides removed, the incidence of RLNIZ LNM was 31.3%, which was not rare. The metastatic rate of lymph nodes in RLNIZ was lower than that (46.84%) reported by Tian et al. (15), which might be due to the different definitions of RLNIZ (0.5 cm from the outer edge of the lymph node to the RLN entrance point by Tian et al.) and sample sizes between the studies. The common locations of lymph nodes in RLNIZ were shown in **Figure 3**. As for the patients with recurrent disease in the central compartment, the rate of recurrent disease to RLNIZ was 12.1%.

More importantly, RLNIZ LNM was correlated with several poor prognostic factors, including larger tumor size, increased number of CNLNM, and lateral node metastasis. Thus, it means that lymph nodes in RLNIZ were usually involved in patients with heavy tumor burden. Given that metastatic lymph nodes in RLNIZ were usually too small to be detected preoperatively at primary surgery, the abilities of those related risk factors predicting RLNIZ LNM were studied. As shown in **Table 4**, patients with CNLNM and lateral node metastasis were respectively 4.8 and 3.8 times more likely to suffer from RLNIZ LNM. In addition, RLNIZ LNM was also associated with age less

**TABLE 3** | Characteristics of patients with recurrent nodal disease in RLNIZ.

| Case number | Age/ sex | Time to relapse | Surgery | Location and size of recurrent nodal disease in RLNIZ | Complications |
|---|---|---|---|---|---|
| 1 | 59/F | 6 years | Left CND; Left LND | Left 1.9 × 1.0 cm | No |
| 2 | 59/M | 2 years | Bilateral CND; Right LND; | Left 0.9 × 0.7cm | No |
| 3 | 46/F | 10 years | Bilateral CND; Bilateral LND; Parapharyngeal lymph nodes dissection | Right 0.5 × 0.5 cm | Right vocal cord paralysis |
| 4 | 16/M | 6 months | Residual thyroidectomy; Bilateral CND; Bilateral LND | Left 0.7 × 0.5cm | No |

*RLNIZ, recurrent laryngeal nerve inlet zone; CND, central neck dissection; LND, lateral neck dissection; F, female; M, male.*

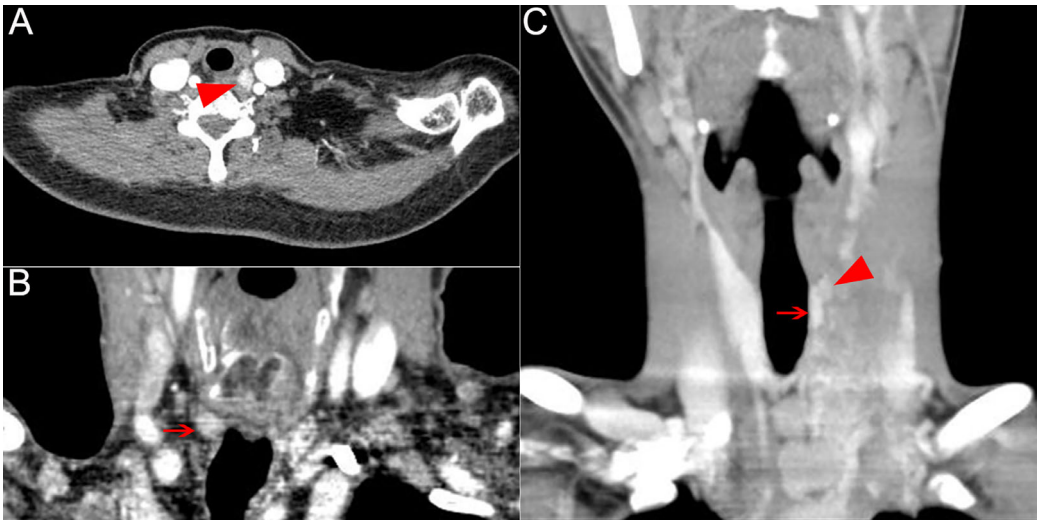


**FIGURE 2** | Recurrent nodal disease in RLNIZ diagnosed by enhanced computer tomography. **(A)** Recurrent nodal disease in RLNIZ in case 1. **(B)** Residual thyroid tissue in RLNIZ without tumor foci. **(C)** Recurrent nodal disease and residual thyroid tissue with tumor foci in RLNIZ in case 4. Red arrowhead: recurrent nodal disease; red arrow: residual thyroid tissue. RLNIZ, recurrent laryngeal nerve inlet zone.

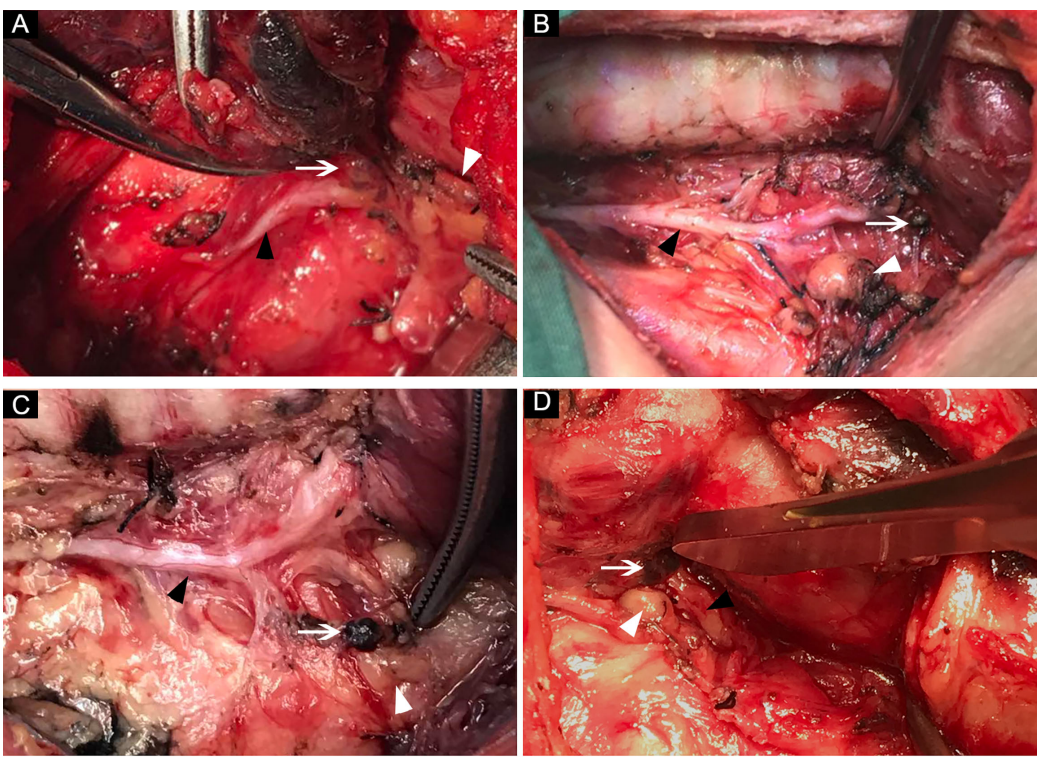


**FIGURE 3** | The common locations of lymph nodes in RLNIZ. **(A)** Lymph node located medially to the RLN inlet; **(B)** small lymph node located laterally to the RLN inlet; **(C)** lymph node located far from RLN inlet due the traction; **(D)** lymph node and SPG located closely to each other at RLNIZ. White arrow: lymph nodes in RLNIZ; black arrow head: RLN; white arrowhead: superior parathyroid gland. RLNIZ, recurrent laryngeal nerve inlet zone; RLN, recurrent laryngeal nerve; SPG, superior parathyroid gland.

**TABLE 4** | Ability of age<45 years, tumor size>1 cm, potential CNLNM and lateral nodes metastasis to predict RLNIZ lymph nodes metastasis.

| | Sensitivity | Specificity | PPV | NPV | LR+ | LR- |
|---|---|---|---|---|---|---|
| Age<45 years | 50 | 81.8 | 66 | 70 | 2.7 | 0.6 |
| Tumor size >1 cm | 44.1 | 76.9 | 55.3 | 68 | 1.9 | 0.7 |
| Further CNLNM* | 51.3 | 89.2 | 83 | 64.1 | 4.8 | 0.8 |
| Lateral nodes metastasis | 85.7 | 77.5 | 38.3 | 97.1 | 3.8 | 0.2 |

*RLNIZ, recurrent laryngeal nerve inlet zone; CNLNM, central neck lymph nodes metastasis.*
*PPV, positive predictive value; NPV, negative predictive value.*
*LR+, positive likelihood ratio; LR–, negative likelihood ratio.*
**Patients with only metastatic disease to RLNIZ in central compartment were excluded.*

than 45 years. This result agreed with that of a study by Wang et al. (16) which showed an increased lymph node positivity among young patients with PTC. Although older age was considered as a high risk factor for decreased cancer-specific survival, patients younger than 45 years had worse outcomes than older patients within stage II (AJCC staging protocol) (17). Those results indicated that RLNIZ LNM would more likely occur in patients with PTC who suffer heavy disease burden, especially in patients younger than 45 years. Therefore, more attention should be paid to the dissection of lymph nodes in RLNIZ to reduce the risk of structural recurrence in the central compartment in those patients.

It must be noted that RLNIZ dissection may be deliberately omitted by un-experienced surgeons in attempt to reduce the morbidity of RLN and parathyroid gland injury. A study by Zhang et al. (18) showed that the major mechanism of RLN injury was thermal injury, at a distal 1-cm below the inlet of RLN, during thyroidectomy. Liu et al. (19) reported that excessive stretch of thyroid lobe played an important role in RLN injury near the entry point of RLN, whereas, RLN injury in this region usually occurred in the procedure of thyroidectomy rather than lymph nodes dissection. In our cohort, no RLN injury during primary surgery was observed. Hypoparathyroidism should alarm the surgeon in the procedure of RLNIZ dissection. About 80% of SPGs were generally located within a 2-cm region about 1 cm above the crossing point of RLN and inferior thyroid artery, which could be easily identified and then protected (20). Rodrigues et al. (21) reported that 11.1% right SPG were located medially to RLN. Hence, some of SPGs can be found in RLNIZ (**Figure 3D**), which are more difficult to protect. In our cohort, 1.8% of SPGs were inadvertently removed during RLNIZ dissection, which may add to the risk of permanent hypothyroidism in patients undergoing bilateral CND. Transient hypoparathyroidism occurred in nine of 152 patients (5.9%), and no permanent hypoparathyroidism was noted after the primary surgery. Therefore, RLNIZ dissection can be performed safely by experienced surgeons at initial surgery.

In order to evaluate the significance of RLNIZ node metastasis, we included patients with recurrence disease in the same period time of the study because of the relatively indolent biological behavior of PTC which needed a long period of follow-up. In our cohort, the rate of recurrence of nodal disease in RLNIZ was 12.1%, which was not rare. Vocal cord paralysis was a major concern in those patients who needed a surgical reintervention in the central compartment. About 2–17.8% permanent RLN injury occurs in CND revision (11, 14). In our cohort, one of four patients (25%) with structural recurrence in RLNIZ suffered permanent vocal cord paralysis after reintervention for CND. Tian et al. (15) reported two cases of structural recurrence in RLNIZ, and both resulted in hoarseness after reoperation. Management of recurrent disease in RLNIZ requires meticulous dissection of the RLN. Intraoperative RLN monitoring could aid in nerve identification and protection (22). Given the tight adhesion and fibrosis in RLNIZ, only when recurrent nodal disease in RLNIZ is diagnosed preoperatively should RLNIZ dissection be performed in order to decrease the risk for iatrogenic RLN injury. Surgical approach from the lateral side of strap muscles may be optimal to access the RLNIZ.

Although no hypoparathyroidism was observed in the four patients undergoing reintervention in our study, hypoparathyroidism is still a potential complication in revised CND. The incidence of temporary and permanent hypoparathyroidism in reinterventions is reported to be 46.3–60% and 2–4.6%, respectively (11, 23). Since SPG is located near RLNIZ and is vulnerable to injury during removal of recurrent disease in RLNIZ, only recurrent disease or suspected lymph nodes in RLNIZ should be excised to decrease the risk of permanent hypoparathyroidism, on the premise that SPG may not be identified intraoperatively. When SPG is identified or auto-transplanted intraoperatively, any adipose tissues in or near RLNIZ should be excised radically.

In the evaluation of structural recurrence in RLNIZ, it is difficult to distinguish between residual thyroid tissue from metastatic lymph nodes (**Figure 2B**). Usually, thyroid remnants in RLNIZ were left by some surgeons with the purpose of reducing the morbidity of RLN injury at initial surgery. However, the presence of thyroid remnants is a substantial risk factor for predicting central compartment recurrence after salvage CND (14). In patients undergoing reintervention, 88.6% of thyroid remnants contained residual malignancy (14), which may add to the risk of metastatic disease to RLNIZ (**Figure 2C**) and invasion to RLN (11). Thus, given that the incidence of residual malignancy is high in the patients undergoing reintervention, total thyroidectomy of a lobe should be performed with the assurance of surgical safety.

This study has some limitations. Firstly, this is a retrospective study with relatively small sample, which might bias the findings of the current study. Secondly, the follow-up time was relatively short to precisely evaluate the effect of RLNIZ dissection on the recurrence of PTC after initial surgery. Thus, a larger well-designed prospective study with longer follow-up should be performed to further confirm the significance of RLNIZ dissection in PTC. Thirdly, the relationship between RLNIZ LNM and pathological subtype of PTC was not evaluated since

such data could not be obtained from the pathology reports of these study patients. Highly invasive subtypes of PTC may contribute to the accuracy of the analysis for the relationships between RLNIZ LNM and clinicopathological factors. Fourthly, as the information of primary tumors of four patients with recurrent disease in RLNIZ was unknown, the correlation between primary tumor and recurrent nodal disease in RLNIZ could not be evaluated. Lastly, the number of patients with recurrent PTC disease admitted to our institution was small which may explain the lower rate of the recurrent disease in RLNIZ compared to results by Clayman et al. (14). This may lead to undervaluation of the morbidity of complications when reinterventions are needed for recurrent disease in RLNIZ.

In summary, this study provided valuable information regarding the involvement of RLNIZ lymph nodes in patients with PTC at initial surgery. Although the lymph nodes in RLNIZ adjacent to important anatomical structures such as RLN and SPG, RLNIZ dissection can be performed safely by experienced surgeons. The study results suggest that RLNIZ LNM is associated with several poor prognostic factors, and CNLNM and lateral node metastases were highly predictive of RLNIZ LNM. This is helpful for surgeons in optimizing the extent of CND at initial surgery in the patients with heavy tumor burden with a goal of reducing recurrence rate. Structural recurrent disease in RLNIZ is of substantial risk for RLN injury which may be avoided by intentional RLNIZ dissection at initial surgery. Studies with long-term follow-up are needed to affirm conclusions on outcomes and prognosis.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Committee of Ethics in Research of Affiliated Yantai Yuhuangding Hospital of Qingdao University. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

GZ, XS, WY, and HZ contributed to conception and design of the study. GW organized the database. HS performed the statistical analysis. GZ wrote the first draft of the manuscript. CM, YG, and DW wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

This work was funded by the Taishan Scholars Program of Shandong Province (NO.ts20190991).

## REFERENCES

1. eng JW, Yang XH, Wu BQ, Sun DL, Jiang Y and Qu Z. Predictive Factors for Central Lymph Node and Lateral Cervical Lymph Node Metastases in Papillary Thyroid Carcinoma. *Clin Transl Oncol* (2019) 21:1482–91. doi: 10.1007/s12094-019-02076-0
2. Xu SY, Yao JJ, Zhou W, Chen L and Zhan WW. Clinical Characteristics and Ultrasonographic Features for Predicting Central Lymph Node Metastasis in Clinically Node-Negative Papillary Thyroid Carcinoma Without Capsule Invasion Thyroid Carcinoma Without Capsule Invasion. *Head Neck* (2019) 41:3984–91. doi: 10.1002/hed.25941
3. Liu C, Xiao C, Chen J, Li X, Feng Z, Gao Q and Liu Z. Risk Factor Analysis for Predicting Cervical Lymph Node Metastasis in Papillary Thyroid Carcinoma: A Study of 966 Patients. *BMC Cancer* (2019) 19:622. doi: 10.1186/s12885-019-5835-6
4. Lee YC, Na SY, Park GC, Han JH, Kim SW and Eun YG. Occult Lymph Node Metastasis and Risk of Regional Recurrence in Papillary Thyroid Cancer After Bilateral Prophylactic Central Neck Dissection: A Multi-Institutional Study. *Surgery* (2017) 161:465–71. doi: 10.1016/j.surg.2016.07.031
5. Kim H, Kim TH, Choe JH, Kim JH, Kim JS, Oh YL, et al. Patterns of Initial Recurrence in Completely Resected Papillary Thyroid Carcinoma. *Thyroid* (2017) 27:908–14. doi: 10.1089/thy.2016.0648
6. Wang LY, Migliacci JC, Tuttle RM, Shaha AR, Shah JP, Patel SG and Ganly I. Management and Outcome of Clinically Evident Neck Recurrence in Patients With Papillary Thyroid Cancer. *Clin Endocrinol (Oxf)* (2017) 87:566–71. doi: 10.1111/cen.13378
7. Kruijff S, Petersen JF, Chen P, Aniss AM, Clifton-Bligh RJ, Sidhu SB, et al. Patterns of Structural Recurrence in Papillary Thyroid Cancer. *World J Surg* (2014) 38:653–9. doi: 10.1007/s00268-013-2286-0
8. Dong W, Horiuchi K, Tokumitsu H, Sakamoto A, Noguchi E, Ueda Y and Okamoto T. Time-Varying Pattern of Mortality and Recurrence From Papillary Thyroid Cancer: Lessons From a Long-Term Follow-Up. *Thyroid* (2019) 29:802–8. doi: 10.1089/thy.2018.0128
9. Ryu YJ, Cho JS, Park MH and Yoon JH. Identifying Risk Factors of Recurrence for Clinically Node Negative Papillary Thyroid Carcinoma With Pathologic N1a. *BMC Surg* (2019) 19:78. doi: 10.1186/s12893-019-0541-5
10. Ahn D, Lee GJ and Sohn JH. Recurrence Following Hemithyroidectomy in Patients With Low- and Intermediate-Risk Papillary Thyroid Carcinoma. *Br J Surg* (2020) 107:687–94. doi: 10.1002/bjs.11430
11. Roh JL, Kim JM and Park CI. Central Compartment Reoperation for Recurrent/Persistent Differentiated Thyroid Cancer: Patterns of Recurrence, Morbidity, and Prediction of Postoperative Hypocalcemia. *Ann Surg Oncol* (2011) 18:1312–8. doi: 10.1245/s10434-010-1470-9
12. Bates MF, Lamas MR, Randle RW, Long KL, Pitt SC, Schneifer DF and Sippel RS. Back So Soon? Is Early Recurrence of Papillary Thyroid Cancer Really Just Persistent Disease? *Surgery* (2018) 163:118–23. doi: 10.1016/j.surg.2017.05.028
13. Siraj AK, Parvathareddy SK, Qadri Z, Siddiqui K, Al-Sobhi SS, Al-Dayel F and Al-Kuraya KS. Annual Hazard Rate of Recurrence in Middle Eastern Papillary Thyroid Cancer Over a Long-Term Follow-Up. *Cancers (Basel)* (2020) 12: E3624. doi: 10.3390/cancers12123624
14. Clayman GL, Agarwal G, Edeiken BS, Waguespack SG, Roberts DB and Sherman SI. Long-Term Outcome of Comprehensive Central Compartment Dissection in Patients With Recurrent/Persistent Papillary Thyroid Carcinoma. *Thyroid* (2011) 21:1309–16. doi: 10.1089/thy.2011.0170
15. Lv T, Liu Z and Yan J. Lymph Node Metastasis Around the Entrance Point to Recurrent Laryngeal Nerve in Papillary Thyroid Carcinoma. *Sci Rep* (2020) 10:5433. doi: 10.1038/s41598-020-62031-w
16. Jiang C, Liu S, Zhu Z, Fang J, Zheng X, Hong S and Wang S. Young Age Increases the Risk of Lymph Node Positivity in Papillary Thyroid Cancer Patients: A SEER Data-Based Study. *Cancer Manag Res* (2018) 10:3867–73. doi: 10.2147/CMAR.S167774
17. Tran Cao HS, Johnston LE, Chang DC and Bouvet M. A Critical Analysis of the American Joint Committee on Cancer (AJCC) Staging System for Differentiated Thyroid Carcinoma in Young Patients on the Basis of the

Surveillance, Epidemiology, and End Results (SEER) Registry. *Surgery* (2012) 152:145–51. doi: 10.1016/j.surg.2012.02.015
18. Zhang D, Sun H, Tufano R, Caruso E, Dionigi G and Kim HY. Recurrent Laryngeal Nerve Management in Transoral Endoscopic Thyroidectomy. *Oral Oncol* (2020) 108:104755. doi: 10.1016/j.oraloncology.2020.104755
19. Liu N, Chen B, Li L, Zeng Q, Sheng L, Zhang B, et al. Mechanisms of Recurrent Laryngeal Nerve Injury Near the Nerve Entry Point During Thyroid Surgery: A Retrospective Cohort Study. *Int J Surg* (2020) 83:125–30. doi: 10.1016/j.ijsu.2020.08.058
20. Taterra D, Wong LM, Vikse J, Sanna B, Pękala P, Walocha J, et al. The Prevalence and Anatomy of Parathyroid Glands: A Meta-Analysis With Implications for Parathyroid Surgery. *Langenbecks Arch Surg* (2019) 404:63–70. doi: 10.1007/s00423-019-01751-8
21. Hojaij F, Vanderlei F, Plopper C, Rodrigues CJ, Jácomo A, Cernea C, et al. Parathyroid Gland Anatomical Distribution and Relation to Anthropometric and Demographic Parameters: A Cadaveric Study. *Anat Sci Int* (2011) 86:204–12. doi: 10.1007/s12565-011-0111-0
22. Wu CW, Dionigi G, Barczynski M, Chiang FY, Dralle H, Schneider R, et al. International Neuromonitoring Study Group Guidelines 2018: Part Ii: Optimal Recurrent Laryngeal Nerve Management for Invasive Thyroid Cancer-Incorporation of Surgical, Laryngeal, and Neural Electro physiologic Data. *Laryngoscope* (2018) 128(Suppl 3):S18–27. doi: 10.1002/lary.27360
23. Pereira JA, Jimeno J, Miquel J, Iglesias M, Munné A, Sancho JJ, et al. Nodal Yield, Morbidity, and Recurrence After Central Neck Dissection for Papillary Thyroid Carcinoma. *Surgery* (2005) 138:1095–1100, discussion 1100-1101. doi: 10.1016/j.surg.2005.09.013

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

# Advantages of publishing in Frontiers

**OPEN ACCESS**
Articles are free to read for greatest visibility and readership

**FAST PUBLICATION**
Around 90 days from submission to decision

**HIGH QUALITY PEER-REVIEW**
Rigorous, collaborative, and constructive peer-review

**TRANSPARENT PEER-REVIEW**
Editors and reviewers acknowledged by name on published articles

**Frontiers**
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

**Visit us:** www.frontiersin.org
**Contact us:** frontiersin.org/about/contact

**REPRODUCIBILITY OF RESEARCH**
Support open data and methods to enhance research reproducibility

**DIGITAL PUBLISHING**
Articles designed for optimal readership across devices

**FOLLOW US**
@frontiersin

**IMPACT METRICS**
Advanced article metrics track visibility across digital media

**EXTENSIVE PROMOTION**
Marketing and promotion of impactful research

**LOOP RESEARCH NETWORK**
Our network increases your article's readership