

World Journal of *Clinical Cases*

World J Clin Cases 2020 April 26; 8(8): 1343-1560





GUIDELINES

- 1343** Prevention program for the COVID-19 in a children's digestive endoscopy center
Ma XP, Wang H, Bai DM, Zou Y, Zhou SM, Wen FQ, Dai DL

REVIEW

- 1350** Predictive factors for central lymph node metastases in papillary thyroid microcarcinoma
Wu X, Li BL, Zheng CJ, He XD
- 1361** Probiotic mixture VSL#3: An overview of basic and clinical studies in chronic diseases
Cheng FS, Pan D, Chang B, Jiang M, Sang LX

MINIREVIEWS

- 1385** Hypertransaminasemia in the course of infection with SARS-CoV-2: Incidence and pathogenetic hypothesis
Zippi M, Fiorino S, Occhigrossi G, Hong W
- 1391** Stability and infectivity of coronaviruses in inanimate environments
Ren SY, Wang WB, Hao YG, Zhang HR, Wang ZC, Chen YL, Gao RD
- 1400** Status, challenges, and future prospects of stem cell therapy in pelvic floor disorders
Cheng J, Zhao ZW, Wen JR, Wang L, Huang LW, Yang YL, Zhao FN, Xiao JY, Fang F, Wu J, Miao YL

ORIGINAL ARTICLE

Retrospective Study

- 1414** Bedside score predicting retained common bile duct stone in acute biliary pancreatitis
Khoury T, Kadah A, Mahamid M, Mari A, Sbeit W

Observational Study

- 1424** Clinicopathological differences and correlations between right and left colon cancer
Kalantzis I, Nonni A, Pavlakis K, Delicha EM, Miltiadou K, Kosmas C, Ziras N, Gkoumas K, Gakiopoulou H
- 1444** Hemodynamic characteristics in preeclampsia women during cesarean delivery after spinal anesthesia with ropivacaine
Zhao N, Xu J, Li XG, Walline JH, Li YC, Wang L, Zhao GS, Xu MJ

CASE REPORT

- 1454** Mucosa-associated lymphoid tissue lymphoma simulating Crohn's disease: A case report
Stundiene I, Maksimaityte V, Liakina V, Valantinas J

- 1463** Suicide attempt using potassium tablets for congenital chloride diarrhea: A case report
Iijima S
- 1471** Embolization of pancreatic arteriovenous malformation: A case report
Yoon SY, Jeon GS, Lee SJ, Kim DJ, Kwon CI, Park MH
- 1477** Novel frameshift mutation in the SACS gene causing spastic ataxia of charlevoix-saguenay in a consanguineous family from the Arabian Peninsula: A case report and review of literature
Al-Ajmi A, Shamsah S, Janicijevic A, Williams M, Al-Mulla F
- 1489** Duodenal mature teratoma causing partial intestinal obstruction: A first case report in an adult
Chansoon T, Angkathunyakul N, Aroonroch R, Jirasiritham J
- 1495** Rare anaplastic sarcoma of the kidney: A case report
Kao JL, Tsung SH, Shiao CC
- 1502** Unusual association of Axenfeld-Rieger syndrome and wandering spleen: A case report
Chang YL, Lin J, Li YH, Tsao LC
- 1507** Primary cutaneous mantle cell lymphoma: Report of a rare case
Zheng XD, Zhang YL, Xie JL, Zhou XG
- 1515** Typical ulcerative colitis treated by herbs-partitioned moxibustion: A case report
Lin YY, Zhao JM, Ji YJ, Ma Z, Zheng HD, Huang Y, Cui YH, Lu Y, Wu HG
- 1525** Bronchogenic cyst of the stomach: A case report
He WT, Deng JY, Liang H, Xiao JY, Cao FL
- 1532** Laparoscopic umbilical trocar port site endometriosis: A case report
Ao X, Xiong W, Tan SQ
- 1538** Unusual presentation of congenital radioulnar synostosis with osteoporosis, fragility fracture and nonunion: A case report and review of literature
Yang ZY, Ni JD, Long Z, Kuang LT, Tao SB
- 1547** Hydatidiform mole in a scar on the uterus: A case report
Jiang HR, Shi WW, Liang X, Zhang H, Tan Y
- 1554** Pulmonary contusion mimicking COVID-19: A case report
Chen LR, Chen ZX, Liu YC, Peng L, Zhang Y, Xu Q, Lin Q, Tao YM, Wu H, Yin S, Hu YJ

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Steven M Schwarz, MD, Professor, Department of Pediatrics, SUNY-Downstate Medical Center, Brooklyn, NY 11203, United States

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The WJCC is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2019 Edition of Journal Citation Reports cites the 2018 impact factor for WJCC as 1.153 (5-year impact factor: N/A), ranking WJCC as 99 among 160 journals in Medicine, General and Internal (quartile in category Q3).

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: Ji-Hong Liu

Proofing Production Department Director: Xiang Li

Responsible Editorial Office Director: Jin-Lai Wang

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Semimonthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Bao-Gan Peng, Sandro Vento

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

April 26, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Predictive factors for central lymph node metastases in papillary thyroid microcarcinoma

Xin Wu, Bing-Lu Li, Chao-Ji Zheng, Xiao-Dong He

ORCID number: Xin Wu (0000-0002-3839-4768); Bing-Lu Li (0000-0002-9142-0793); Chao-Ji Zheng (0000-0002-8989-2556); Xiao-Dong He (0000-0002-4761-9199).

Author contributions: All authors helped to write the paper; Wu X wrote the manuscript and analyzed the data; Li BL contributed to the conception and design of the paper and analyzed the data; Zheng CJ and He XD contributed to the writing of the manuscript and the conception and design of the paper.

Supported by Fundamental Research Funds for the Central Universities of China, No. 3332019022.

Conflict-of-interest statement: The authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited Manuscript

Received: January 11, 2020

Xin Wu, Bing-Lu Li, Chao-Ji Zheng, Xiao-Dong He, Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Corresponding author: Bing-Lu Li, MD, Professor, Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 1, Shuaifuyuan, Dongcheng District, Beijing 100730, China. pumchlib-inglu@163.com

Abstract

Papillary thyroid microcarcinoma (PTMC) measures 1 cm or less in its longest dimension. The incidence of PTMC is increasing worldwide. Surgery is the primary treatment; however, prophylactic central lymph node dissection is controversial, and discrepancies between different guidelines have been noted. Routine prophylactic central lymph node dissection may result in hypoparathyroidism and recurrent laryngeal nerve injury in some patients without lymph node metastasis, while simple thyroidectomy may leave metastatic lymph nodes in high-risk patients. To selectively perform prophylactic lymph node dissections in high-risk patients, it is important to identify predictive factors for lymph node metastases in patients with PTMC. Several studies have reported on this, but their conclusions are not entirely consistent. Several clinicopathologic characteristics have been identified as risk factors for central lymph node metastases, and the most commonly reported factors include age, gender, tumor size and location, multifocality, bilaterality, extrathyroidal extension, and abnormal lymph node found using ultrasound. Here, we provide an overview of previous studies along with a favorable opinion on or against these factors, with the aim of increasing the understanding of this topic among the medical community. In addition, current opinions about prophylactic central lymph node dissection are reviewed and discussed.

Key words: Papillary thyroid carcinoma; Papillary thyroid microcarcinoma; Central lymph node dissection; Prophylactic; Risk factor; Prognosis

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Surgery is the primary treatment for papillary thyroid microcarcinoma. Prophylactic central lymph node dissection is controversial due to its potential oncologic benefit and side effects. This review provides an overview of previous studies on the predictive factors for lymph node metastases in patients with papillary thyroid

Peer-review started: January 11, 2020

First decision: February 26, 2020

Revised: March 4, 2020

Accepted: April 4, 2020

Article in press: April 4, 2020

Published online: April 26, 2020

P-Reviewer: Coskun A

S-Editor: Wang YQ

L-Editor: Wang TQ

E-Editor: Liu MY



microcarcinoma. The most commonly reported factors include age, gender, tumor size and location, multifocality, bilaterality, extrathyroidal extension, and abnormal lymph node found using ultrasound. Prophylactic central neck dissection should be selectively performed only in high-risk patients.

Citation: Wu X, Li BL, Zheng CJ, He XD. Predictive factors for central lymph node metastases in papillary thyroid microcarcinoma. *World J Clin Cases* 2020; 8(8): 1350-1360

URL: <https://www.wjgnet.com/2307-8960/full/v8/i8/1350.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v8.i8.1350>

INTRODUCTION

The incidence of thyroid carcinoma is increasing worldwide. In 2015, over 62000 and 90000 patients were diagnosed with thyroid cancer in the United States and China, respectively^[1,2]. However, the mortality from thyroid carcinoma has changed little over the past several decades^[1]. Different subtypes of thyroid carcinoma demonstrate completely different clinical behaviors. Indolent tumors and aggressive malignancies should be treated using a different therapeutic approach. Differentiated thyroid carcinoma is the most common type of thyroid carcinoma, and papillary thyroid carcinoma (PTC) is the most common subtype of differentiated thyroid carcinoma. Papillary thyroid microcarcinoma (PTMC) is defined as a PTC measuring 1 cm or less in its longest dimension and has a disease-specific mortality rate, local recurrence rate, and distant metastases rate of < 1%, 2%-6%, and 1%-2%, respectively^[3-6]. The excellent prognosis may be related to the indolent nature of PTMC. Some prospective clinical studies reported that only a few PTMC patients showed tumor progression after long-term observation^[7,8]. Surgery remains to be the primary treatment method; however, the treatment pattern, especially the extent of surgery, is controversial, and discrepancies between different guidelines have been observed^[6,9-11]. An important point of contention is the need for prophylactic central lymph node dissection in PTMC. Routine prophylactic central neck dissection may result in recurrent laryngeal nerve injury and hypoparathyroidism in some patients without lymph node metastasis. Conversely, simple thyroidectomy may leave metastatic lymph nodes in high-risk patients. Therefore, it is necessary to identify predictive factors for lymph node metastases in patients with PTMC and to selectively perform prophylactic lymph node dissections in high-risk patients. In this paper, we review the published literature on possible predictive factors for central lymph node metastases in PTMC patients, with the aim of increasing the understanding of this topic among the medical community.

PREDICTIVE FACTORS

Several different predictive factors for central lymph node metastases in patients with PTMC have been reported. These mainly include three aspects: Demographic characteristics, ultrasonography features, and pathological results. The most commonly reported factors include age, gender, tumor size and location, multifocality, bilaterality, extrathyroidal extension, and abnormal lymph node found using ultrasound. We will review each of these factors below.

Age

Age is a very important factor in the staging system for thyroid carcinoma. The latest American Joint Committee on Cancer (AJCC) TNM staging system utilizes age as an important basis for staging^[12]. Moreover, previous studies indicated that age was a risk factor for central lymph node metastases in patients with PTMC^[13-17]; however, the age threshold varied between the studies. Luo *et al*^[18] studied 1031 patients with PTMC and reported that people aged ≤ 40 years were prone to central lymph node metastases. Yin *et al*^[19] retrospectively reviewed 1092 PTMC patients and found that the age of < 45 years was an independent predictor of central lymph node metastases. Wang *et al*^[20] conducted a study on 8668 PTMC patients and revealed that the age of < 55 years was significantly associated with central lymph node metastases. One of our published reports revealed that age < 45 years was an independent risk factor for central lymph node metastases in patients with PTMC^[21]. Despite the variability in the

cut-off value for age, the consensus is that young patients have more lymph node metastases than older patients. While focusing on the relationship between age and lymph node metastases, many studies examined the relationship between age and disease prognosis. Some studies reported that a cut-off of 55 years was much more suitable than 45 years as the predictive factor for disease-specific survival of PTC patients^[22-29]. Moreover, the AJCC staging system increased the cut-off age at diagnosis from 45 years to 55 years in its eighth edition^[12]. Interestingly, most studies indicate that young age is a risk factor for lymph node metastases, while older age is linked to a poor prognosis. A high rate of lymph node metastases is therefore not equal to a poor prognosis. In general, elderly patients tend to have more age-dependent physiological changes, weaker health, and more complications that result in a worse prognosis than younger patients.

Gender

In women, the incidence of PTMC is much higher but the rate of lymph node metastases is lower than in men^[30]. The higher levels of progesterone and estrogen in women than in men can affect the pituitary gonadotropin-releasing hormone levels and result in this phenomenon^[31,32]. Concurrently, the higher basal metabolic rate of men may incite an overactive proliferation of tumor cells, which makes men more prone to metastases than women. Zhang *et al*^[33] conducted a retrospective analysis of 1304 cases and reported that being male was an independent predictor of central lymph node metastases in cN0 PTMC patients. In addition, Zheng *et al*^[34] indicated that being male was an independent risk factor for central lymph node metastases in PTMC. Numerous other studies confirmed the association between male gender and lymph node metastases in PTMC^[35-37]. Nonetheless, the association between sex and PTMC remains controversial. Jeon *et al*^[38] demonstrated that being male was not an independent risk factor, and Jiang *et al*^[39] found no relationship between central lymph node metastases and sex in cN0 PTC patients. In addition to sex and lymph node metastases, researchers studied the relationship between sex and prognosis. Lee *et al*^[40] studied 2930 patients with PTC in a single institution and found that men with PTC had higher rates of recurrence and mortality than women, but there were no differences in disease-free survival rates between the two sexes of patients with PTMC. Thus, in patients with PTMC, sex plays different roles in lymph node metastases and prognosis.

Tumor size

Tumor size is a very important characteristic in most tumor staging systems. For PTC, the definition of T-stage is shown in Table 1. All PTMC patients belong to stage T1a (tumor ≤ 1 cm limited to the thyroid). As early detection of PTMC is the main reason for the rapid increase in the incidence rates of thyroid carcinoma^[15,41], researchers hope to stratify the size of PTMC in further detail. When relationships between tumor size and lymph node metastases were studied, several different sizes were quoted. In their study which included 673 patients with PTMC, Jin *et al*^[42] revealed that a tumor size of > 5 mm was an independent predictor of central lymph node metastases. Moreover, Yu *et al*^[43] retrospectively studied 917 patients with PTMC and found that a large tumor size (> 5 mm) was an independent factor in the prediction of central lymph node metastases in PTMC patients. A meta-analysis of 19 studies involving 8345 PTMC patients demonstrated that central lymph node metastases were associated with large tumor size (> 5 mm)^[44]. A cut-off of 5 mm is accepted and recommended by most published studies^[16,18,20,33,35]. In addition, some other sizes have been acknowledged by different studies. Lee *et al*^[45] studied 275 patients with PTMC and found that a tumor size of ≤ 7 mm was less likely to be associated with aggressive features than a tumor size of > 7 mm and recommended a cut-off of 7 mm as the threshold of PTMC tumor size. Zheng *et al*^[34] assessed thresholds greater than 8 mm, 7 mm, 6 mm, 5 mm, and 4 mm and concluded that a tumor size of > 6 mm significantly correlated with central lymph node metastases in PTMC. Gui *et al*^[14] used 5.75 mm as the threshold, while Xu *et al*^[15] deduced the size to be that of 7 mm. Nevertheless, the consensus is that the smaller the tumor, the lower the probability of lymph node metastases. Moreover, tumor size significantly correlates with tumor prognosis. To ensure correct and predictable prognosis of small-sized PTMC, the United Kingdom National Multidisciplinary Guidelines recommended against thyroid stimulating hormone suppression treatment in solitary PTMC with a tumor size of ≤ 5 mm and without the presence of adverse risk factors (being symptomatic, positron emission tomography positivity, extrathyroidal extension, poorly differentiation, desmoplastic fibrosis, and/or infiltrative growth pattern)^[10].

Tumor location

The thyroid gland is composed of two lobes and an isthmus, and sometimes, a

Table 1 The definition of T-stage for papillary thyroid carcinoma

T category	T criteria
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤ 1 cm in greatest dimension limited to the thyroid
T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension limited to the thyroid
T2	Tumor > 2 cm but ≤ 4 cm in greatest dimension limited to the thyroid
T3	Tumor > 4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a	Tumor > 4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size

According to the American Joint Committee on Cancer 2018 TNM classification, 8th edition.

pyramidal lobe is present. For lesions in the right and left lobes, tumor location is described as the upper portion (upper than the high plane of the isthmus), the middle portion (parallel to the isthmus), and the lower portion (lower than the low plane of the isthmus). Alternatively, tumor location is described as upper third, middle third, and lower third. Tumors at different locations have different tendencies of lymphatic metastases. Zhang *et al*^[46] followed 1066 consecutive PTMC patients over a 5 year period and revealed that for PTMC patients with a solitary tumor, the upper portion was associated with a high risk of lateral lymph node metastases but a low risk of central lymph node metastases. Xu *et al*^[47] found that in PTMC patients with a solitary tumor, the lower portion was associated with a high risk of central lymph node metastases. Luo *et al*^[18] found that the lower portion was related to a high risk of central lymph node metastases while the upper portion conferred a high risk of lateral lymph node metastases. In addition, Jin *et al*^[42] reported that the lower portion was an independent risk factor for central lymph node metastases. In a previous study, we found that the tumor location (upper portion) was an independent risk factor for lateral neck lymph node metastases in patients with PTMC^[48]. Different rates of lymphatic metastases among different tumor locations may be related to different lymphatic flow pathways. Tumor cells from the lower portion are easily transported to the pretracheal and paratracheal lymph nodes *via* the lymphatic flow along the inferior thyroid vein, while lesions of the upper portion are easily transported to the lateral neck lymph nodes *via* lymphatic flow along the superior thyroid artery^[49,50]. A full understanding of the relationship between tumor location and lymphatic metastases is important in determining the extent of lymph node dissection.

Multifocality

If more than one focus is found in bilateral or unilateral thyroid gland lobes, the tumor is considered to be multifocal. This phenomenon is observed in approximately 20%–40% of patients with PTMC^[51–55]. Multifocality is considered as increased development of independent cancers or intraglandular spread of the primary focus^[56–59]. Although most tumor staging systems do not include multifocality, it is considered as an independent risk factor for lymph node metastases in patients with PTMC^[14,15,17,18,60]. Zheng *et al*^[61] studied 3543 patients with PTMC and found that multifocality with ≥ 3 tumor foci was a risk factor for central lymph node metastases in PTMC. Similarly, Guo *et al*^[62] reported that multifocality was associated with a high risk of central lymph node metastases in PTMC. Additionally, a meta-analysis study revealed the same phenomenon^[44]. Conversely, Zhou *et al*^[63] concluded that multifocality was not significantly related to central lymph node metastases in multivariate analysis. Lee *et al*^[64] reported that multifocality was not a risk factor for central lymph node metastases. Thus, there is a lack of consensus on the relationship between multifocality and central lymph node metastases. In addition to lymph node metastases, the association between multifocality and prognosis has been studied. Some previous studies found that multifocality was significantly associated with

tumor recurrence^[51,53], but other studies showed no direct relationship between multifocality and tumor recurrence in PTMC^[54,65]. The prognostic value of multifocality in PTMC needs to be confirmed through further research.

Bilaterality

Bilaterality is a special situation of multifocality, and over 80% of multifocality cases are associated with bilaterality^[33,63]. It has been reported that bilaterality could increase the rate of lymph node metastases in PTMC^[33-35,66]. Kim *et al*^[67] retrospectively reviewed 5656 patients with PTMC and found that bilaterality was an independent risk factor for a high prevalence of central lymph node metastases. Kim *et al*^[68] studied 483 PTMC patients and found that bilaterality was significantly associated with central lymph node metastases. Conversely, several studies revealed a negative result of the association between bilaterality and lymph node metastases. Yang *et al*^[69] retrospectively studied 291 patients and found no relationship between bilaterality and central lymph node metastases. A meta-analysis that included 14 studies and 4573 patients reported that an elevated risk of central lymph node metastases was associated with multifocality but not with bilaterality^[70]. Another meta-analysis of 25 studies involving 7719 patients revealed that bilaterality was not significantly associated with central lymph node metastases^[71]. Debates on this topic are ongoing. Different patient selection criteria and statistical methods could result in contradicting conclusions. Moreover, the complex lymphatic flow pathways of the thyroid may play an interfering role.

Extrathyroidal extension

Extrathyroidal extension in PTMC includes various extents of invasion such as the perithyroid tissues, strap muscles, recurrent laryngeal nerves, trachea, esophagus, larynx, prevertebral fascia, and mediastinal vessels. Several studies have reported that extrathyroidal extension was a risk factor for central lymph node metastases in PTMC^[46,47,72,73]. Both Gülben *et al*^[74] and Wang *et al*^[75] reported that thyroid capsular invasion was an independent risk factor for lymph node metastases. Varshney *et al*^[76] studied 685 consecutive patients and found that there was a significant association between extrathyroidal extension and lymph node metastases. The extrathyroidal extension means that tumor cells have broken through the thyroid gland, which increases the probability of lymph node metastases. However, accurate diagnosis of the extension is challenging since the thyroid gland does not have a well-defined true capsule and the thyroid gland capsule is made up of inconspicuous thin fibrous tissues^[34]. Additionally, it is controversial whether minor extension identified only on histological examination has a different effect on metastases and prognosis in PTMC as compared to gross extrathyroidal extension. The latest AJCC TNM staging system highlighted that gross extrathyroidal extension was an unfavorable prognostic factor and downplayed the significance of minor extension^[12]. Nonetheless, Gui *et al*^[14] examined 541 PTMC patients and found that the rate of microscopic extrathyroidal extension was significantly different between patients with and without lymph node metastases. Future studies are warranted on the differences in clinical manifestations and molecular mechanisms between minor and gross extensions.

Abnormal lymph node detected by ultrasound

Ultrasonography is the most effective and convenient preoperative thyroid examination. Metastatic lymph nodes are often round in shape, with loss of fatty hilum, calcification in the cortex, cystic changes, hypoechogenicity, and peripheral vascularity^[6,77,78]. However, it is very difficult to achieve a satisfactory rate of diagnosis prior to surgery because the exploration of central lymph nodes is significantly affected by glands, bones, and gas^[79]. Several studies reported that the sensitivity of ultrasonography in identifying central lymph node metastases was quite low^[73,80,81]. Yu *et al*^[43] reported that less than 30% of central lymph node metastases confirmed by frozen section in patients with PTMC could be diagnosed by preoperative ultrasonography. Moreover, our previous study found that only 21% of central lymph node metastases could be correctly diagnosed by preoperative ultrasonography^[21]. Additionally, Ito *et al*^[30] reported a preoperative ultrasonography sensitivity of just 10.9%. Conversely, the specificity of preoperative ultrasonography is quite high^[21,79]. Huang *et al*^[82] reported that ultrasonography has sensitivity and specificity rates of 12.5% and 95.2%, respectively, for the evaluation of lymph nodes. Lee *et al*^[83] studied 184 consecutive PTC patients and found that ultrasound had a specificity of 88.4% in assessing central lymph nodes. Therefore, the possibility of metastases is very high if an abnormal lymph node is detected on ultrasound. Nevertheless, ultrasound is an affordable and noninvasive procedure that is easy to perform. Other imaging modalities such as computed tomography, positron emission tomography, and magnetic resonance imaging have all been recommended as an adjunct to

ultrasound^[6].

Other factors

In addition to the most commonly reported factors discussed above, some other factors have been reported. Luo *et al*^[18] revealed that a sum of the maximum diameter of multifocal lesions of ≥ 8.5 mm in the unilateral lobe was prone to central lymph node metastases in PTMC. In addition, they reported that the probability of lateral lymph node metastases increases with an increase in the sum of the maximum diameter of multifocal lesions in a unilateral lobe. The authors, therefore, stated that attention should be paid to multifocal lesions and the sum of their maximum diameter in PTMC patients. Wang *et al*^[20] reported that lateral lymph node metastases were significantly associated with central lymph node metastases. Jin *et al*^[42] found that BRAF mutation was an independent predictor of central lymph node metastases. These factors have attracted great attention and been studied by several researchers.

PROPHYLACTIC CENTRAL NECK DISSECTION

For PTC, the definition of N-stage is shown in Table 2. The central compartment (level VI) contains pretracheal, paratracheal, and prelaryngeal lymph nodes. Central compartment lymph node dissection should be performed superior to the hyoid bone, inferior to the innominate (brachiocephalic) artery, and lateral to the carotid sheaths. In clinical practice, central neck dissection in thyroid carcinoma can be divided into therapeutic dissection and prophylactic dissection. Therapeutic central compartment lymph node dissection is recommended and routinely performed in PTC patients with clinically positive lymph nodes^[6,84,85]. However, the use of prophylactic central compartment lymph node dissection is controversial, especially in PTMC patients with clinically negative lymph nodes^[6,10,11,86,87]. Aggressive treatment often increases complications such as hypoparathyroidism and recurrent laryngeal nerve injury, while conservative treatment may result in an increased rate of recurrence.

Many researchers have studied and reported the clinical effects of prophylactic central neck dissection. Kim *et al*^[88] performed a randomized clinical trial and followed 164 PTMC patients for a mean duration of 73.4 mo. They found that prophylactic ipsilateral central neck dissection did not provide any oncological benefit for PTMC patients with clinically negative lymph nodes. Xu *et al*^[89] studied 611 consecutive patients and concluded that routine prophylactic central compartment lymph node dissection was not a protective factor for lateral neck recurrence-free survival in patients with PTMC and clinically negative lymph nodes. Similarly, several meta-analyses^[90-92] did not support prophylactic central neck dissection in PTMC patients without clinical lymph node metastases due to a lack of high-level evidence in favor of the procedure. In contrast, some researchers advocated for prophylactic central neck dissection due to the high rates of occult metastatic lymph nodes in clinical negative patients^[30,93,94]. Su *et al*^[95] conducted a meta-analysis which highlighted that thyroidectomy plus prophylactic central neck dissection may reduce recurrence rates in patients with PTMC. Another meta-analysis that included five studies with 1132 patients reported that prophylactic central neck dissection does not increase the permanent morbidity rate such as hypocalcemia and vocal cord palsy^[96].

The oncologic benefit of routine prophylactic central neck dissection is still controversial. It is essential to identify high-risk patients prior to surgery and to subsequently perform prophylactic central neck dissection in selected patients. The various guidelines currently available provide different treatment options. The American Thyroid Association recommends prophylactic central neck dissection for patients with advanced primary tumors (T3 or T4) or clinical positive lateral lymph nodes metastases (cN1b)^[6]. Furthermore, it clarifies that thyroidectomy without prophylactic central neck dissection is an appropriate indication for PTC patients with noninvasive, clinically node-negative, and small primary tumors (T1 or T2)^[6]. The European Society of Endocrine Surgeons suggests that prophylactic central neck dissection should be risk-stratified^[11]. The potential risk factors include large tumors (T3 or T4), age ≥ 45 years or ≤ 15 years, male sex, bilaterality or multifocality, and involvement of lateral lymph nodes^[11]. The United Kingdom National Multidisciplinary Guidelines indicated that prophylactic central neck dissection is associated with a high incidence of long-term permanent hypoparathyroidism and recurrent laryngeal nerve damage and therefore, not recommend prophylactic central neck dissection in low-risk and small papillary carcinomas^[10]. Conversely, the Chinese Association of Thyroid Oncology and Chinese Anti-Cancer Association recommends prophylactic central lymph node dissection for cN0 PTMC patients^[9]. Nonetheless, it emphasizes the importance of parathyroid gland and recurrent laryngeal nerve

Table 2 The definition of N-stage for papillary thyroid carcinoma

N category	N criteria
Nx	Regional lymph nodes cannot be assessed
N0	No evidence of locoregional lymph node metastasis
N0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1	Metastasis to regional nodes
N1a	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease
N1b	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (level I, II, III, IV, or V) or retropharyngeal lymph nodes

According to the American Joint Committee on Cancer 2018 TNM classification, 8th edition.

protection^[9].

CONCLUSION

Many clinicopathologic factors have been studied as predictors of central lymph node metastases in patients with PTMC. The most interesting and commonly discussed factors include age, gender, tumor size and location, multifocality, bilaterality, extrathyroidal extension, and abnormal lymph node on ultrasound. Studies have been published with a favorable opinion on or against each of these factors. To preoperatively assess whether a PTMC patient is at high risk for lymph node metastases, the presence of a combination of different factors is required. Prophylactic central neck dissection is a controversial procedure and should only be performed selectively in high-risk patients.

REFERENCES

- 1 **Cabanillas ME**, McFadden DG, Durante C. Thyroid cancer. *Lancet* 2016; **388**: 2783-2795 [PMID: 27240885 DOI: 10.1016/S0140-6736(16)30172-6]
- 2 **Chen W**, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115-132 [PMID: 26808342 DOI: 10.3322/caac.21338]
- 3 **Mazzaferri EL**. Management of low-risk differentiated thyroid cancer. *Endocr Pract* 2007; **13**: 498-512 [PMID: 17872353 DOI: 10.4158/EP.13.5.498]
- 4 **Hay ID**. Management of patients with low-risk papillary thyroid carcinoma. *Endocr Pract* 2007; **13**: 521-533 [PMID: 17872355 DOI: 10.4158/EP.13.5.521]
- 5 **Tang J**, Liu HB, Yu L, Meng X, Leng SX, Zhang H. Clinical-pathological Characteristics and Prognostic Factors for Papillary Thyroid Microcarcinoma in the Elderly. *J Cancer* 2018; **9**: 256-262 [PMID: 29344271 DOI: 10.7150/jca.22700]
- 6 **Haugen BR**, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 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 [PMID: 26462967 DOI: 10.1089/thy.2015.0020]
- 7 **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* 2014; **24**: 27-34 [PMID: 24001104 DOI: 10.1089/thy.2013.0367]
- 8 **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**: 1222-1231 [PMID: 20066418 DOI: 10.1007/s00268-009-0359-x]
- 9 **Gao M**, Ge M, Ji Q, Cheng R, Lu H, Guan H, Gao L, Guo Z, Huang T, Huang X, Li X, Lin Y, Liu Q, Ni X, Pan Y, Qin J, Shan Z, Sun H, Wang X, Xu Z, Yu Y, Zhao D, Zhang N, Zhang S, Zheng Y, Zhu J, Li D, Zheng X. Chinese Association Of Thyroid Oncology Cato Chinese Anti-Cancer Association. 2016 Chinese expert consensus and guidelines for the diagnosis and treatment of papillary thyroid microcarcinoma. *Cancer Biol Med* 2017; **14**: 203-211 [PMID: 28948061 DOI: 10.20892/j.issn.2095-3941.2017.0051]
- 10 **Mitchell AL**, Gandhi A, Scott-Coombes D, Perros P. Management of thyroid cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016; **130**: S150-S160 [PMID: 27841128 DOI: 10.1017/S0022215116000578]
- 11 **Sancho JJ**, Lennard TW, Paunovic I, Triponez F, Sitges-Serra A. Prophylactic central neck dissection in papillary thyroid cancer: a consensus report of the European Society of Endocrine Surgeons (ESES). *Langenbecks Arch Surg* 2014; **399**: 155-163 [PMID: 24352594 DOI: 10.1007/s00423-013-1152-8]
- 12 **Tuttle RM**, Morris LF, Haugen BR, Shah JP, Sosa JA, Rohren E, Subramaniam RM, Hunt JL, Perrier ND. Thyroid - Differentiated and Anaplastic Carcinoma. In: *AJCC Cancer Staging Manual*. 8th ed. New York:

- Springer, 2017: 873-890
- 13 **Wang X**, Tan J, Zheng W, Li N. A retrospective study of the clinical features in papillary thyroid microcarcinoma depending on age. *Nucl Med Commun* 2018; **39**: 713-719 [PMID: [29762261](#) DOI: [10.1097/MNM.0000000000000859](#)]
 - 14 **Gui CY**, Qiu SL, Peng ZH, Wang M. Clinical and pathologic predictors of central lymph node metastasis in papillary thyroid microcarcinoma: a retrospective cohort study. *J Endocrinol Invest* 2018; **41**: 403-409 [PMID: [28884301](#) DOI: [10.1007/s40618-017-0759-y](#)]
 - 15 **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**: 128-134 [PMID: [29229118](#) DOI: [10.1016/j.jss.2017.08.007](#)]
 - 16 **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 [PMID: [31275239](#) DOI: [10.3389/fendo.2019.00363](#)]
 - 17 **Yuan J**, Li J, Chen X, Lin X, Du J, Zhao G, Chen Z, Wu Z. Identification of risk factors of central lymph node metastasis and evaluation of the effect of prophylactic central neck dissection on migration of staging and risk stratification in patients with clinically node-negative papillary thyroid microcarcinoma. *Bull Cancer* 2017; **104**: 516-523 [PMID: [28476312](#) DOI: [10.1016/j.bulcan.2017.03.005](#)]
 - 18 **Luo Y**, Zhao Y, Chen K, Shen J, Shi J, Lu S, Lei J, Li Z, Luo D. Clinical analysis of cervical lymph node metastasis risk factors in patients with papillary thyroid microcarcinoma. *J Endocrinol Invest* 2019; **42**: 227-236 [PMID: [29876836](#) DOI: [10.1007/s40618-018-0908-y](#)]
 - 19 **Yin X**, Liu C, Guo Y, Li X, Shen N, Zhao X, Yu P, Wang S, Liu Z. Influence of tumor extent on central lymph node metastasis in solitary papillary thyroid microcarcinomas: a retrospective study of 1092 patients. *World J Surg Oncol* 2017; **15**: 133 [PMID: [28716127](#) DOI: [10.1186/s12957-017-1202-8](#)]
 - 20 **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 [PMID: [29803769](#) DOI: [10.1016/j.ijssu.2018.05.023](#)]
 - 21 **Wu X**, Li B, Zheng C, He X. Risk factors for central lymph node metastases in patients with papillary thyroid microcarcinoma. *Endocr Pract* 2018; **24**: 1057-1062 [PMID: [30289307](#) DOI: [10.4158/EP-2018-0305](#)]
 - 22 **Nixon IJ**, Kuk D, Wreesmann V, Morris L, Palmer FL, Ganly I, Patel SG, Singh B, Tuttle RM, Shaha AR, Gönen M, Shah JP. Defining a Valid Age Cutoff in Staging of Well-Differentiated Thyroid Cancer. *Ann Surg Oncol* 2016; **23**: 410-415 [PMID: [26215199](#) DOI: [10.1245/s10434-015-4762-2](#)]
 - 23 **Nixon IJ**, Wang LY, Migliacci JC, Eskander A, Campbell MJ, Aniss A, Morris L, Vaisman F, Corbo R, Momesso D, Vaisman M, Carvalho A, Learoyd D, Leslie WD, Nason RW, Kuk D, Wreesmann V, Morris L, Palmer FL, Ganly I, Patel SG, Singh B, Tuttle RM, Shaha AR, Gönen M, Pathak KA, Shen WT, Sywak M, Kowalski L, Freeman J, Perrier N, Shah JP. 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**: 373-380 [PMID: [26914539](#) DOI: [10.1089/thy.2015.0315](#)]
 - 24 **Ganly I**, Nixon IJ, Wang LY, Palmer FL, Migliacci JC, Aniss A, Sywak M, Eskander AE, Freeman JL, Campbell MJ, Shen WT, Vaisman F, Momesso D, Corbo R, Vaisman M, Shaha A, Tuttle RM, Shah JP, Patel SG. Survival from Differentiated Thyroid Cancer: What Has Age Got to Do with It? *Thyroid* 2015; **25**: 1106-1114 [PMID: [26148759](#) DOI: [10.1089/thy.2015.0104](#)]
 - 25 **Hendrickson-Rebizant J**, Sigvaldason H, Nason RW, Pathak KA. Identifying the most appropriate age threshold for TNM stage grouping of well-differentiated thyroid cancer. *Eur J Surg Oncol* 2015; **41**: 1028-1032 [PMID: [25986855](#) DOI: [10.1016/j.ejso.2015.04.014](#)]
 - 26 **Ito Y**, Fukushima M, Tomoda C, Inoue H, Kihara M, Higashiyama T, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Miyauchi A. Prognosis of patients with papillary thyroid carcinoma having clinically apparent metastasis to the lateral compartment. *Endocr J* 2009; **56**: 759-766 [PMID: [19506324](#) DOI: [10.1507/endocrj.k09e-025](#)]
 - 27 **Ito Y**, Ichihara K, Masuoka H, Fukushima M, Inoue H, Kihara M, Tomoda C, Higashiyama T, Takamura Y, Kobayashi K, Miya A, Miyauchi A. Establishment of an intraoperative staging system (iStage) by improving UICC TNM classification system for papillary thyroid carcinoma. *World J Surg* 2010; **34**: 2570-2580 [PMID: [20625728](#) DOI: [10.1007/s00268-010-0710-2](#)]
 - 28 **Kim SJ**, Myong JP, Suh H, Lee KE, Youn YK. Optimal Cutoff Age for Predicting Mortality Associated with Differentiated Thyroid Cancer. *PLoS One* 2015; **10**: e0130848 [PMID: [26102084](#) DOI: [10.1371/journal.pone.0130848](#)]
 - 29 **Mazurat A**, Torroni A, Hendrickson-Rebizant J, Benning H, Nason RW, Pathak KA. The age factor in survival of a population cohort of well-differentiated thyroid cancer. *Endocr Connect* 2013; **2**: 154-160 [PMID: [24008393](#) DOI: [10.1530/EC-13-0056](#)]
 - 30 **Ito Y**, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K, Miyauchi A. Clinical significance of metastasis to the central compartment from papillary microcarcinoma of the thyroid. *World J Surg* 2006; **30**: 91-99 [PMID: [16369721](#) DOI: [10.1007/s00268-005-0113-y](#)]
 - 31 **Shindo H**, Amino N, Ito Y, Kihara M, Kobayashi K, Miya A, Hirokawa M, Miyauchi A. Papillary thyroid microcarcinoma might progress during pregnancy. *Thyroid* 2014; **24**: 840-844 [PMID: [24397849](#) DOI: [10.1089/thy.2013.0527](#)]
 - 32 **Rahbari R**, Zhang L, Kebebew E. Thyroid cancer gender disparity. *Future Oncol* 2010; **6**: 1771-1779 [PMID: [21142662](#) DOI: [10.2217/fon.10.127](#)]
 - 33 **Zhang Q**, Wang Z, Meng X, Duh QY, Chen G. Predictors for central lymph node metastases in CN0 papillary thyroid microcarcinoma (mPTC): A retrospective analysis of 1304 cases. *Asian J Surg* 2019; **42**: 571-576 [PMID: [30348606](#) DOI: [10.1016/j.asjsur.2018.08.013](#)]
 - 34 **Zheng X**, Peng C, Gao M, Zhi J, Hou X, Zhao J, Wei X, Chi J, Li D, Qian B. Risk factors for cervical lymph node metastasis in papillary thyroid microcarcinoma: a study of 1,587 patients. *Cancer Biol Med* 2019; **16**: 121-130 [PMID: [31119052](#) DOI: [10.20892/j.issn.2095-3941.2018.0125](#)]
 - 35 **Cheng F**, Chen Y, Zhu L, Zhou B, Xu Y, Chen Y, Wen L, Chen S. Risk Factors for Cervical Lymph Node Metastasis of Papillary Thyroid Microcarcinoma: A Single-Center Retrospective Study. *Int J Endocrinol* 2019; **2019**: 8579828 [PMID: [30774660](#) DOI: [10.1155/2019/8579828](#)]
 - 36 **Tao Y**, Wang C, Li L, Xing H, Bai Y, Han B, Liu Z, Yang X, Zhu S. Clinicopathological features for predicting central and lateral lymph node metastasis in papillary thyroid microcarcinoma: Analysis of 66 cases that underwent central and lateral lymph node dissection. *Mol Clin Oncol* 2017; **6**: 49-55 [PMID: [28123728](#) DOI: [10.3892/mco.2016.1085](#)]
 - 37 **Lu ZZ**, Zhang Y, Wei SF, Li DS, Zhu QH, Sun SJ, Li M, Li LI. Outcome of papillary thyroid

- microcarcinoma: Study of 1,990 cases. *Mol Clin Oncol* 2015; **3**: 672-676 [PMID: [26137285](#) DOI: [10.3892/mco.2015.495](#)]
- 38 **Jeon MJ**, Kim WG, Choi YM, Kwon H, Lee YM, Sung TY, Yoon JH, Chung KW, Hong SJ, Kim TY, Shong YK, Song DE, Kim WB. Features Predictive of Distant Metastasis in Papillary Thyroid Microcarcinomas. *Thyroid* 2016; **26**: 161-168 [PMID: [26563473](#) DOI: [10.1089/thy.2015.0375](#)]
 - 39 **Jiang LH**, Chen C, Tan Z, Lu XX, Hu SS, Wang QL, Hou XX, Cao J, Ge MH. Clinical Characteristics Related to Central Lymph Node Metastasis in cN0 Papillary Thyroid Carcinoma: A Retrospective Study of 916 Patients. *Int J Endocrinol* 2014; **2014**: 385787 [PMID: [25214837](#) DOI: [10.1155/2014/385787](#)]
 - 40 **Lee YH**, Lee YM, Sung TY, Yoon JH, Song DE, Kim TY, Baek JH, Ryu JS, Chung KW, Hong SJ. Is Male Gender a Prognostic Factor for Papillary Thyroid Microcarcinoma? *Ann Surg Oncol* 2017; **24**: 1958-1964 [PMID: [28130621](#) DOI: [10.1245/s10434-017-5788-4](#)]
 - 41 **Davies L**, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA* 2006; **295**: 2164-2167 [PMID: [16684987](#) DOI: [10.1001/jama.295.18.2164](#)]
 - 42 **Jin WX**, Ye DR, Sun YH, Zhou XF, Wang OC, Zhang XH, Cai YF. Prediction of central lymph node metastasis in papillary thyroid microcarcinoma according to clinicopathologic factors and thyroid nodule sonographic features: a case-control study. *Cancer Manag Res* 2018; **10**: 3237-3243 [PMID: [30233240](#) DOI: [10.2147/CMAR.S169741](#)]
 - 43 **Yu X**, Song X, Sun W, Zhao S, Zhao J, Wang YG. Independent Risk Factors Predicting Central Lymph Node Metastasis in Papillary Thyroid Microcarcinoma. *Horm Metab Res* 2017; **49**: 201-207 [PMID: [28351086](#) DOI: [10.1055/s-0043-101917](#)]
 - 44 **Qu N**, Zhang L, Ji QH, Chen JY, Zhu YX, Cao YM, Shen Q. Risk Factors for Central Compartment Lymph Node Metastasis in Papillary Thyroid Microcarcinoma: A Meta-Analysis. *World J Surg* 2015; **39**: 2459-2470 [PMID: [26099728](#) DOI: [10.1007/s00268-015-3108-3](#)]
 - 45 **Lee KJ**, Cho YJ, Kim SJ, Lee SC, Kim JG, Ahn CJ, Lee DH. Analysis of the clinicopathologic features of papillary thyroid microcarcinoma based on 7-mm tumor size. *World J Surg* 2011; **35**: 318-323 [PMID: [21153817](#) DOI: [10.1007/s00268-010-0886-5](#)]
 - 46 **Zhang L**, Wei WJ, Ji QH, Zhu YX, Wang ZY, Wang Y, Huang CP, Shen Q, Li DS, Wu Y. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. *J Clin Endocrinol Metab* 2012; **97**: 1250-1257 [PMID: [22319042](#) DOI: [10.1210/jc.2011-1546](#)]
 - 47 **Xu D**, Lv X, Wang S, Dai W. Risk factors for predicting central lymph node metastasis in papillary thyroid microcarcinoma. *Int J Clin Exp Pathol* 2014; **7**: 6199-6205 [PMID: [25337270](#)]
 - 48 **Wu X**, Li B, Zheng C, He X. Predicting factors of lateral neck lymph node metastases in patients with papillary thyroid microcarcinoma. *Medicine (Baltimore)* 2019; **98**: e16386 [PMID: [31277195](#) DOI: [10.1097/MD.00000000000016386](#)]
 - 49 **Zeng RC**, Li Q, Lin KL, Zhang W, Gao EL, Huang GL, Zhang XH, Zheng MH. Predicting the factors of lateral lymph node metastasis in papillary microcarcinoma of the thyroid in eastern China. *Clin Transl Oncol* 2012; **14**: 842-847 [PMID: [22872517](#) DOI: [10.1007/s12094-012-0875-2](#)]
 - 50 **Ito Y**, Tomoda C, Urano T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K, Miyauchi A. Papillary microcarcinoma of the thyroid: how should it be treated? *World J Surg* 2004; **28**: 1115-1121 [PMID: [15490053](#) DOI: [10.1007/s00268-004-7644-5](#)]
 - 51 **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 [PMID: [12833452](#) DOI: [10.1002/ncr.11442](#)]
 - 52 **Lombardi CP**, Bellantone R, De Crea C, Paladino NC, Fadda G, Salvatori M, Raffaelli M. 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**: 1214-1221 [PMID: [20052467](#) DOI: [10.1007/s00268-009-0375-x](#)]
 - 53 **Qu N**, Zhang L, Ji QH, Zhu YX, Wang ZY, Shen Q, Wang Y, Li DS. Number of tumor foci predicts prognosis in papillary thyroid cancer. *BMC Cancer* 2014; **14**: 914 [PMID: [25471041](#) DOI: [10.1186/1471-2407-14-914](#)]
 - 54 **Kim KJ**, Kim SM, Lee YS, Chung WY, Chang HS, Park CS. Prognostic significance of tumor multifocality in papillary thyroid carcinoma and its relationship with primary tumor size: a retrospective study of 2,309 consecutive patients. *Ann Surg Oncol* 2015; **22**: 125-131 [PMID: [25092159](#) DOI: [10.1245/s10434-014-3899-8](#)]
 - 55 **Usluogullari CA**, Onal ED, Ozdemir E, Ucler R, Kiyak G, Ersoy PE, Yalcin S, Güler G, Ersoy R, Cakir B. A retrospective analysis of prognostic factors predictive of lymph-node metastasis and recurrence in thyroid papillary microcarcinoma. *Minerva Endocrinol* 2015; **40**: 15-22 [PMID: [24699706](#)]
 - 56 **Mazeh H**, Samet Y, Hochstein D, Mizrahi I, Ariel I, Eid A, Freund HR. Multifocality in well-differentiated thyroid carcinomas calls for total thyroidectomy. *Am J Surg* 2011; **201**: 770-775 [PMID: [20864083](#) DOI: [10.1016/j.amjsurg.2010.03.004](#)]
 - 57 **Sun W**, Lan X, Zhang H, Dong W, Wang Z, He L, Zhang T, Liu S. Risk Factors for Central Lymph Node Metastasis in CN0 Papillary Thyroid Carcinoma: A Systematic Review and Meta-Analysis. *PLoS One* 2015; **10**: e0139021 [PMID: [26431346](#) DOI: [10.1371/journal.pone.0139021](#)]
 - 58 **Jovanovic L**, Delahunt B, McIver B, Eberhardt NL, Grebe SK. Most multifocal papillary thyroid carcinomas acquire genetic and morphotype diversity through subclonal evolution following the intra-glandular spread of the initial neoplastic clone. *J Pathol* 2008; **215**: 145-154 [PMID: [18393366](#) DOI: [10.1002/path.2342](#)]
 - 59 **Jung CK**, Kang YG, Bae JS, Lim DJ, Choi YJ, Lee KY. Unique patterns of tumor growth related with the risk of lymph node metastasis in papillary thyroid carcinoma. *Mod Pathol* 2010; **23**: 1201-1208 [PMID: [20543822](#) DOI: [10.1038/modpathol.2010.116](#)]
 - 60 **Mercante G**, Frasoldati A, Pedroni C, Formisano D, Renza L, Piana S, Gardini G, Valcavi R, Barbieri V. 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**: 707-716 [PMID: [19348581](#) DOI: [10.1089/thy.2008.0270](#)]
 - 61 **Zheng W**, Wang K, Wu J, Wang W, Shang J. Multifocality is associated with central neck lymph node metastases in papillary thyroid microcarcinoma. *Cancer Manag Res* 2018; **10**: 1527-1533 [PMID: [29942154](#) DOI: [10.2147/CMAR.S163263](#)]
 - 62 **Guo Y**, Liu Z, Yu P, Liu C, Ming J, Zhang N, Yusufu M, Chen C, Huang T. Using foci number to predict central lymph node metastases of papillary thyroid microcarcinomas with multifocality. *Int J Clin Exp Med* 2015; **8**: 9925-9930 [PMID: [26309677](#)]
 - 63 **Zhou YL**, Gao EL, Zhang W, Yang H, Guo GL, Zhang XH, Wang OC. 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 [PMID: [22540396](#) DOI: [10.1186/1477-7819-10-67](#)]
- 64 **Lee SH**, Lee SS, Jin SM, Kim JH, Rho YS. Predictive factors for central compartment lymph node metastasis in thyroid papillary microcarcinoma. *Laryngoscope* 2008; **118**: 659-662 [PMID: [18176339](#) DOI: [10.1097/MLG.0b013e318161f9d1](#)]
- 65 **Mehanna H**, Al-Maqbili T, Carter B, Martin E, Campain N, Watkinson J, McCabe C, Boelaert K, Franklyn JA. 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**: 2834-2843 [PMID: [24828487](#) DOI: [10.1210/jc.2013-2118](#)]
- 66 **Zhao Q**, Ming J, Liu C, Shi L, Xu X, Nie X, Huang T. Multifocality and total tumor diameter predict central neck lymph node metastases in papillary thyroid microcarcinoma. *Ann Surg Oncol* 2013; **20**: 746-752 [PMID: [22972508](#) DOI: [10.1245/s10434-012-2654-2](#)]
- 67 **Kim SK**, Park I, Woo JW, Lee JH, Choe JH, Kim JH, Kim JS. Predictive Factors for Lymph Node Metastasis in Papillary Thyroid Microcarcinoma. *Ann Surg Oncol* 2016; **23**: 2866-2873 [PMID: [27075321](#) DOI: [10.1245/s10434-016-5225-0](#)]
- 68 **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**: 385-391 [PMID: [23073506](#) DOI: [10.1007/s00268-012-1826-3](#)]
- 69 **Yang Y**, Chen C, Chen Z, Jiang J, Chen Y, Jin L, Guo G, Zhang X, Ye T. Prediction of central compartment lymph node metastasis in papillary thyroid microcarcinoma. *Clin Endocrinol (Oxf)* 2014; **81**: 282-288 [PMID: [24483297](#) DOI: [10.1111/cen.12417](#)]
- 70 **Liu LS**, Liang J, Li JH, Liu X, Jiang L, Long JX, Jiang YM, Wei ZX. The incidence and risk factors for central lymph node metastasis in cN0 papillary thyroid microcarcinoma: a meta-analysis. *Eur Arch Otorhinolaryngol* 2017; **274**: 1327-1338 [PMID: [27645473](#) DOI: [10.1007/s00405-016-4302-0](#)]
- 71 **Qu H**, Sun GR, Liu Y, He QS. Clinical risk factors for central lymph node metastasis in papillary thyroid carcinoma: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 2015; **83**: 124-132 [PMID: [25130203](#) DOI: [10.1111/cen.12583](#)]
- 72 **So YK**, Son YI, Hong SD, Seo MY, Baek CH, Jeong HS, Chung MK. Subclinical lymph node metastasis in papillary thyroid microcarcinoma: a study of 551 resections. *Surgery* 2010; **148**: 526-531 [PMID: [20189620](#) DOI: [10.1016/j.surg.2010.01.003](#)]
- 73 **Soares P**, Celestino R, Gaspar da Rocha A, Sobrinho-Simões M. Papillary thyroid microcarcinoma: how to diagnose and manage this epidemic? *Int J Surg Pathol* 2014; **22**: 113-119 [PMID: [24401191](#) DOI: [10.1177/1066896913517394](#)]
- 74 **Gülben K**, Berberoğlu U, Celen O, Mersin HH. Incidental papillary microcarcinoma of the thyroid--factors affecting lymph node metastasis. *Langenbecks Arch Surg* 2008; **393**: 25-29 [PMID: [17690905](#) DOI: [10.1007/s00423-007-0213-2](#)]
- 75 **Wang W**, Gu J, Shang J, Wang K. Correlation analysis on central lymph node metastasis in 276 patients with cN0 papillary thyroid carcinoma. *Int J Clin Exp Pathol* 2013; **6**: 510-515 [PMID: [23412848](#)]
- 76 **Varshney R**, Pakdaman MN, Sands N, Hier MP, Rochon L, Black MJ, Payne RJ. Lymph node metastasis in thyroid papillary microcarcinoma: a study of 170 patients. *J Laryngol Otol* 2014; **128**: 922-925 [PMID: [25226511](#) DOI: [10.1017/S0022215114001704](#)]
- 77 **American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer**, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009; **19**: 1167-1214 [PMID: [19860577](#) DOI: [10.1089/thy.2009.0110](#)]
- 78 **Leboulleux S**, Girard E, Rose M, Travagli JP, Sabbah N, Caillou B, Hartl DM, Lassau N, Baudin E, Schlumberger M. Ultrasound criteria of malignancy for cervical lymph nodes in patients followed up for differentiated thyroid cancer. *J Clin Endocrinol Metab* 2007; **92**: 3590-3594 [PMID: [17609301](#) DOI: [10.1210/jc.2007-0444](#)]
- 79 **Hwang HS**, Orloff LA. Efficacy of preoperative neck ultrasound in the detection of cervical lymph node metastasis from thyroid cancer. *Laryngoscope* 2011; **121**: 487-491 [PMID: [21344423](#) DOI: [10.1002/lary.21227](#)]
- 80 **Choi YJ**, Yun JS, Kook SH, Jung EC, Park YL. Clinical and imaging assessment of cervical lymph node metastasis in papillary thyroid carcinomas. *World J Surg* 2010; **34**: 1494-1499 [PMID: [20372903](#) DOI: [10.1007/s00268-010-0541-1](#)]
- 81 **Trimboli P**, Treglia G, Giovannella L. Preoperative measurement of serum thyroglobulin to predict malignancy in thyroid nodules: a systematic review. *Horm Metab Res* 2015; **47**: 247-252 [PMID: [25384015](#) DOI: [10.1055/s-0034-1395517](#)]
- 82 **Huang XP**, Ye TT, Zhang L, Liu RF, Lai XJ, Wang L, Yang M, Zhang B, Li XY, Liu ZW, Xia Y, Jiang YX. Sonographic features of papillary thyroid microcarcinoma predicting high-volume central neck lymph node metastasis. *Surg Oncol* 2018; **27**: 172-176 [PMID: [29937168](#) DOI: [10.1016/j.suronc.2018.03.004](#)]
- 83 **Lee YJ**, Kim DW, Park HK, Kim DH, Jung SJ, Oh M, Bae SK. Pre-operative ultrasound diagnosis of nodal metastasis in papillary thyroid carcinoma patients according to nodal compartment. *Ultrasound Med Biol* 2015; **41**: 1294-1300 [PMID: [25703430](#) DOI: [10.1016/j.ultrasmedbio.2015.01.003](#)]
- 84 **Keum HS**, Ji YB, Kim JM, Jeong JH, Choi WH, Ahn YH, Tae K. Optimal surgical extent of lateral and central neck dissection for papillary thyroid carcinoma located in one lobe with clinical lateral lymph node metastasis. *World J Surg Oncol* 2012; **10**: 221 [PMID: [23098385](#) DOI: [10.1186/1477-7819-10-221](#)]
- 85 **Sadowski BM**, Snyder SK, Lairmore TC. Routine bilateral central lymph node clearance for papillary thyroid cancer. *Surgery* 2009; **146**: 696-703; discussion 703-705 [PMID: [19789029](#) DOI: [10.1016/j.surg.2009.06.046](#)]
- 86 **Carling T**, Long WD, Udelsman R. Controversy surrounding the role for routine central lymph node dissection for differentiated thyroid cancer. *Curr Opin Oncol* 2010; **22**: 30-34 [PMID: [19864950](#) DOI: [10.1097/CCO.0b013e3183333ac9](#)]
- 87 **Shaha AR**. Prophylactic central compartment dissection in thyroid cancer: a new avenue of debate. *Surgery* 2009; **146**: 1224-1227 [PMID: [19958952](#) DOI: [10.1016/j.surg.2009.10.020](#)]
- 88 **Kim BY**, Choi N, Kim SW, Jeong HS, Chung MK, Son YI. Randomized trial of prophylactic ipsilateral central lymph node dissection in patients with clinically node negative papillary thyroid microcarcinoma. *Eur Arch Otorhinolaryngol* 2020; **277**: 569-576 [PMID: [31664515](#) DOI: [10.1007/s00405-019-05702-3](#)]
- 89 **Xu S**, Liu W, Zhang Z, Liu Y, Xu Z, Liu J. Routine Prophylactic Central Neck Dissection May Not Obviously Reduce Lateral Neck Recurrence for Papillary Thyroid Microcarcinoma. *ORL J*

- Otorhinolaryngol Relat Spec* 2019; **81**: 73-81 [PMID: [31189172](#) DOI: [10.1159/000497407](#)]
- 90 **Bardet S**, Malville E, Rame JP, Babin E, Samama G, De Raucourt D, Michels JJ, Reznik Y, Henry-Amar M. Macroscopic lymph-node involvement and neck dissection predict lymph-node recurrence in papillary thyroid carcinoma. *Eur J Endocrinol* 2008; **158**: 551-560 [PMID: [18362303](#) DOI: [10.1530/EJE-07-0603](#)]
- 91 **Roh JL**, Park JY, Park CI. Total thyroidectomy plus neck dissection in differentiated papillary thyroid carcinoma patients: pattern of nodal metastasis, morbidity, recurrence, and postoperative levels of serum parathyroid hormone. *Ann Surg* 2007; **245**: 604-610 [PMID: [17414610](#) DOI: [10.1097/01.sla.0000250451.59685.67](#)]
- 92 **Zetoune T**, Keutgen X, Buitrago D, Aldailami H, Shao H, Mazumdar M, Fahey TJ, Zarnegar R. Prophylactic central neck dissection and local recurrence in papillary thyroid cancer: a meta-analysis. *Ann Surg Oncol* 2010; **17**: 3287-3293 [PMID: [20596784](#) DOI: [10.1245/s10434-010-1137-6](#)]
- 93 **Ito Y**, Fukushima M, Higashiyama T, Kihara M, Takamura Y, Kobayashi K, Miya A, Miyauchi A. Incidence and predictors of right paraesophageal lymph node metastasis of N0 papillary thyroid carcinoma located in the right lobe. *Endocr J* 2013; **60**: 389-392 [PMID: [23182918](#) DOI: [10.1507/endocrj.ej12-0362](#)]
- 94 **Salter KD**, Andersen PE, Cohen JI, Schuff KG, Lester L, Shindo ML, Sauer D, Gross ND. Central nodal metastases in papillary thyroid carcinoma based on tumor histologic type and focality. *Arch Otolaryngol Head Neck Surg* 2010; **136**: 692-696 [PMID: [20644065](#) DOI: [10.1001/archoto.2010.112](#)]
- 95 **Su H**, Li Y. Prophylactic central neck dissection and local recurrence in papillary thyroid microcarcinoma: a meta-analysis. *Braz J Otorhinolaryngol* 2019; **85**: 237-243 [PMID: [30017872](#) DOI: [10.1016/j.bjorl.2018.05.004](#)]
- 96 **Chisholm EJ**, Kulinskaya E, Tolley NS. Systematic review and meta-analysis of the adverse effects of thyroidectomy combined with central neck dissection as compared with thyroidectomy alone. *Laryngoscope* 2009; **119**: 1135-1139 [PMID: [19358241](#) DOI: [10.1002/lary.20236](#)]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

