CLINICAL AND PARACLINICAL CHARACTERISTICS AND FACTORS ASSOCIATED WITH OCCULT CERVICAL LYMPH NODE METASTASIS IN DIFFERENTIATED THYROID CANCER CT1N0M0 TREATED BY TRANSORAL ENDOSCOPIC THYROIDECTOMY

Nguyen Xuan Hien[1,2,✉], Nguyen Nhat Tan[1], Dang Phuong Chi[1]
Nguyen Gia Hao[1], Le Van Quang[1,2], Nguyen Xuan Hau[1,2,3]
[1]Hanoi Medical University
[2]Hanoi Medical University Hospital
[3]K Hospital

This cross-sectional study analyzed 218 patients diagnosed with cT1N0M0 papillary thyroid carcinoma (PTC) who underwent transoral endoscopic thyroidectomy vestibular approach (TOETVA) at Hanoi Medical University Hospital between January 2020 and December 2023. Patients were classified into two groups based on postoperative pathology: those with occult cervical lymph node metastasis (oCLNM+) and those without (oCLNM−). The mean patient age was 35.3 years, and the majority were female (96.8%). Tumors had a mean size of 6.9mm, were primarily located in a single lobe (87.2%), and were multifocal in 13.8% of cases. Occult lymph node metastasis was identified in 41.3% of patients. Statistical analysis revealed that tumor size greater than 5.5mm and multifocality were significant predictors of oCLNM, with odds ratios of 2.4 (p = 0.028) and higher likelihood of nodal involvement. The median number of harvested lymph nodes was 4 (range: 0 – 22), and the median number of metastatic nodes was 0 (range: 0 – 17). These findings suggest that, even in patients with a clinically negative neck (cN0), there remains a considerable risk of occult lymph node metastases, especially in cases with multifocal tumors and primary tumor size exceeding 5.5mm.

Keywords: TOETVA, Occult cervical lymph node metastasis.

I.INTRODUCTION

Differentiated thyroid cancer (DTC), which includes papillary, follicular, and Hürthle cell subtypes, accounts for the vast majority of thyroid malignancies, making up 90 – 95% of cases.[1] While most patients with localized DTC have an excellent prognosis, with 10-year survival rates exceeding 90%, the presence of lymph node metastasis (LNM) can significantly increase the risk of recurrence and disease-specific mortality. In papillary thyroid carcinoma (PTC), LNM is particularly concerning, as it raises the likelihood of locoregional recurrence, influencing both surgical decisions and the need for adjuvant therapy.[2,3]

One of the greatest challenges in thyroid cancer management is occult cervical lymph node metastasis (oCLNM) - a condition where metastatic lymph nodes are undetected preoperatively in clinically node-negative (cN0) patients. Studies indicate that 20 – 40% of cT1N0M0 DTC patients actually harbor occult nodal metastases, underscoring the need

Corresponding author: Nguyen Xuan Hien
Hanoi Medical University
Email: dr.nguyenxuanhien@gmail.com
Received: 12/05/2025
Accepted: 31/05/2025

for better risk stratification and management strategies.[3-5] Identifying high-risk patients preoperatively can guide surgical planning, ensuring optimal oncologic outcomes while minimizing unnecessary interventions.[5]

Over the past decade, the TOETVA has emerged as a promising minimally invasive alternative to conventional open thyroidectomy, particularly for early-stage DTC.[6] Originally developed for benign thyroid conditions, TOETVA has since been extended to select cancer cases, offering comparable oncologic outcomes with superior cosmetic benefits by avoiding a visible neck scar.

Identifying predictors of oCLNM preoperatively is essential for optimizing surgical decision-making. Integrating tumor size, multifocality, and other risk factors into preoperative risk stratification models could aid surgeons in optimizing the surgical strategy, determining the appropriate extent of resection.[7] Therefore, we conducted this study to describe the clinical and paraclinical characteristics and factors associated with oCLNM in differentiated thyroid cancer cT1N0M0 patients treated by TOETVA.

II. MATERIALS AND METHODS

1. Subjects

This cross-sectional study included 218 patients diagnosed with clinically node-negative (cN0) papillary thyroid carcinoma (PTC) who underwent transoral endoscopic thyroidectomy vestibular approach (TOETVA) at Hanoi Medical University Hospital from January 2020 to December 2023. The inclusion criteria were: (1) histologically confirmed PTC, (2) tumor size ≤ 20 mm, (3) absence of extrathyroidal extension, and (4) no clinically or radiologically detectable lymph node metastasis preoperatively. Exclusion criteria included: (1) previous neck surgery or radiation therapy, (2) evidence of preoperative lymph node metastasis, and (3) incomplete or missing medical records.

2. Methods

Study variables and data analysis

The following clinical and pathological variables were collected and analyzed:

- Demographics: age, gender.
- Ultrasound findings: tumor size (in mm), tumor location (right lobe, left lobe, isthmus, or both lobes), focality (unifocal vs. multifocal), and presence of thyroiditis.
- Surgical data: type of thyroidectomy (total vs. conservative), extent of central neck dissection (unilateral vs. bilateral).
- Pathological data: number of lymph nodes harvested and number of metastatic nodes.
- Outcome variable: presence or absence of occult central lymph node metastasis (oCLNM).

Statistical analyses were performed to identify factors affecting lymph node metastasis. Categorical variables were analyzed using Chi-square or Fisher's exact tests, and continuous variables were compared with the independent t-test. Univariate and multivariate logistic regression analyses assessed prognostic factors for CLNM, reporting odds ratios (ORs) and 95% confidence intervals (CIs). ROC curve analysis determined the optimal tumor size threshold for predicting CLNM. Statistical significance was set at $p < 0.05$, with all analyses conducted using SPSS software (version 22.0).

Surgical procedure

The surgical indications and procedures followed the protocol that we have previously detailed in our earlier publications.[8,9]

3. Research ethics

We will ensure confidentiality of all patients' personal information in this study.

III. RESULTS

Table 1. Clinicopathological characteristics of patients

Variables	Values
Age*	35.3 ± 7.8 (17 - 61)
*Gender*ϕ	
Male	7 (3.2)
Female	211 (96.8)
Tumor size on ultrasound (mm)*	6.9 ± 2.8 (2.5 - 18.0)
Cancer site	
Right lobe	97 (44.5)
Left lobe	93 (42.7)
Isthmus	7 (3.2)
Both lobes	21 (9.6)
*Focality*ϕ	
Multifocal	30 (13.8)
Unifocal	188 (86.2)

**(Mean, Range); ϕ(n, %)*

A total of 218 patients were included in the study. The mean age of the cohort was 35.3 ± 7.8 (17 - 61) years old. The patient population was predominantly female (96.8%), with only 3.2% of patients being male. The mean tumor size on preoperative ultrasound was 6.9 ± 2.8 (2.5 - 18.0) mm, indicating that most tumors were small (≤ 1cm). Tumors were predominantly confined to a single lobe of the thyroid: the right lobe was affected in 97 patients (44.5%) and the left lobe in 93 patients (42.7%). A smaller proportion of cases had tumors involving both lobes (21 patients, 9.6%), and only 7 patients (3.2%) had tumors located in the thyroid isthmus. Most patients presented with unifocal disease (188 patients, 86.2%), whereas 30 patients (13.8%) had multifocal tumors.

Table 2. Surgical outcomes

Variables	Values
Procedure	
Total thyroidectomy + CND	23 (10.6)
Conservative thyroidectomy + CND	195 (89.4)
Central neck dissection	
One side	197 (90.4)
Both side	21 (9.6)
Occult central lymph node metastasis	90 (41.3)

Variables	Values
Number of lymph node (median–range)	
Harvested	4 (0 - 22)
Metastasis	0 (0 - 17)
Metastatic lymph nodes in the oCLNM-positive group (Median-range)	2 (1 - 17)

Among all patients included in the study, total thyroidectomy with central neck dissection (CND) was performed in 23 cases (10.6%), while the majority (195 patients, 89.4%) underwent conservative thyroidectomy with CND. Regarding central neck dissection (CND), one-sided CND was performed in 197 patients (90.4%), whereas bilateral CND was conducted in 21 cases (9.6%). The postoperative lymph node metastasis rate was 41.3% (90/218 patients), indicating a significant proportion of patients with occult cervical lymph node metastasis (oCLNM) despite being clinically node-negative (cN0) preoperatively. The median number of harvested lymph nodes per patient was 4 (range: 0 – 22), while the median number of metastatic lymph nodes was 0 (range: 0 – 17). However, in the subgroup of patients with nodal metastasis, the median number of metastatic lymph nodes was 2.

Table 3. Factors affecting metastatic status of central lymph nodes

Variables	oCLNM –	oCLNM +	OR (95%)	p-value
Gender				
Male	2	5	0.27 (0.51 - 1.42)	0.15
Female	126	85		
Age				
< 45	113	83	0.64 (0.25 - 1.63)	0.35
≥ 45	15	7		
Thyroiditis				
No	109	77	0.97 (0.45 - 2.08)	0.94
Yes	19	13		
Tumor focality				
Unifocal	116	72	2.42 (1.10 - 5.31)	0.028
Multifocal	12	18		

The analysis of factors associated with oCLNM is presented in Table 3. Among the study population, the prevalence of oCLNM was 71.4% in male patients and 40.3% in female patients. Although the proportion appeared higher in males, the odds ratio for gender was 0.27 indicating no statistically significant association between gender and the risk of

oCLNM. Similarly, age and thyroiditis showed no significant correlation with oCLNM with p > 0.05. In contrast, tumor multifocality was significantly associated with oCLNM. Patients with multifocal tumors had a 60.0% oCLNM rate compared to 38.3% in unifocal cases. Logistic regression analysis revealed an OR of 2.42 with p-value equal 0.028, indicating that multifocality is a significant independent predictor of oCLNM in this population.

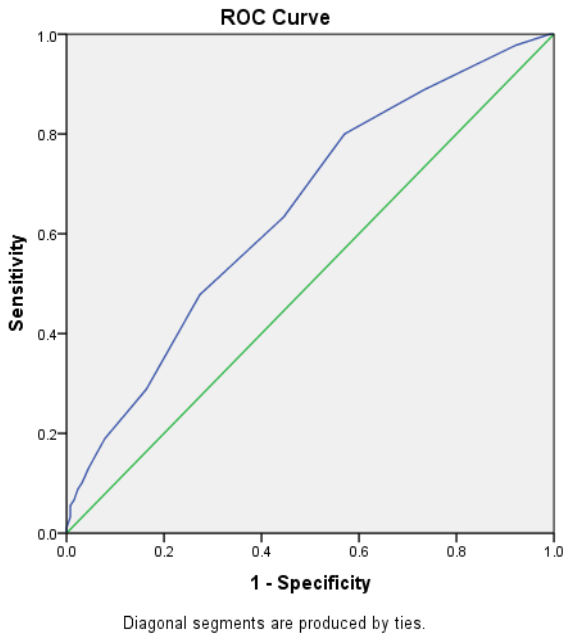

Chart 1. ROC curve illustrating the relationship between the largest tumor size and the likelihood of central neck lymph node metastasis

The receiver operating characteristic (ROC) curve analysis (Chart 1) was used to evaluate the predictive ability of tumor size in determining the presence of oCLNM. The analysis identified an optimal cutoff value of 5.5mm, above which the likelihood of CLNM increased with sensitivity = 0.8, specificity = 0.43. This threshold suggests that patients with tumors exceeding 5.5mm on preoperative ultrasound may have a higher risk of oCLNM.

IV. DISCUSSION

Our study identified a 41.3% incidence of occult cervical lymph node metastasis (oCLNM) in cN0 papillary thyroid carcinoma (PTC) patients undergoing TOETVA, which is consistent with previously reported rates. Prior studies on small, clinically node-negative PTC have documented central compartment metastasis rates ranging from 24% to 35%, with some reports noting incidences as high as 50%.[4] While our observed rate is slightly above the average, it remains within the expected range for early-stage PTC. This slight increase may be attributed to our study's inclusion of prophylactic central neck dissection in all patients, including those with tumors < 10mm.

Notably, our analysis demonstrated two strong independent predictors of oCLNM: tumor multifocality (OR = 2.4, p = 0.028) and tumor size greater than 5.5mm. These factors should be carefully considered when planning surgical strategies, particularly prophylactic central neck dissection, in patients undergoing TOETVA. .Multifocality was significantly associated with oCLNM in our patient cohort, corroborating

findings from several prior studies.[10] Patients with multiple tumor foci are known to have a greater total tumor volume and broader intrathyroidal spread, which likely increases the chance of microscopic nodal involvement.[11,12] Therefore, surgeons should maintain a high index of suspicion for nodal involvement when encountering multifocal disease, even in early-stage, clinically node-negative PTC cases undergoing minimally invasive procedures like TOETVA.

Tumor size emerged as another crucial factor associated with the presence of occult nodal metastasis. Using ROC analysis, we identified a primary tumor diameter of approximately 5.5mm as an optimal cut-off for predicting metastasis. This finding aligns with reports that even within papillary microcarcinomas, those exceeding 5mm carry a significantly greater risk of central node metastasis. Huang et al. (2021) similarly noted that PTC tumors ≥ 5mm had substantially higher odds of nodal spread.[13] Additionally, some retrospective studies have reported varying tumor size cutoff values for predicting central lymph node metastasis. For instance, Yusuf Kayhan et al. (2024) proposed a cutoff of 6.75 mm, while Ling Zhang suggested 6 mm.[14,15] Although there are slight differences in the exact cutoff values, these authors consistently agreed that the risk of occult central lymph node metastasis might be significantly elevated even in patients with small tumors measuring less than 1cm. Consequently, tumor size should serve as a practical criterion to guide preoperative evaluation and decisions regarding the extent of central neck dissection during TOETVA.

In contrast to multifocality and tumor size, patient age, gender, and the presence of thyroiditis did not show statistically significant correlations with oCLNM in our analysis. The lack of significant findings related to age, particularly the cutoff of 45 years, might be attributed to the demographic characteristics of our cohort, predominantly younger females (mean age 35.3 years, 96.8% female). Although the 8th edition of the AJCC/TNM staging system revised the age cutoff from 45 to 55 years to better reflect differences in disease-specific survival, this change primarily affects staging accuracy in advanced-stage disease (i.e., stages III–IV) and long-term survival prediction.[16] In contrast, our study focused on early-stage PTC (cT1N0M0), aiming to identify clinicopathological factors associated with occult central lymph node metastasis (oCLNM). In addition, TOETVA is a relatively recent surgical technique characterized by superior cosmetic outcomes, predominantly younger, female individuals, with very few patients aged ≥ 55 undergoing the procedure. As a result, the 55-year cutoff may lack discriminatory value in this highly skewed population. Multiple recent studies and meta-analyses continue to support the use of 45 years old as a meaningful prognostic threshold in evaluating the risk of CLNM in PTC. A comprehensive meta-analysis involving over 9,000 patients demonstrated that patients younger than 45 had significantly higher odds of CLNM compared to older individuals (OR = 1.59; 95% CI: 1.42 – 1.78).[3] Another analysis focusing on papillary thyroid microcarcinoma (PTMC) cN0 cases also found a higher rate of CLNM in patients aged < 45 (OR = 1.27; 95% CI: 1.08 – 1.48).[17] A large SEER-based population study involving over 48,000 PTC patients revealed a clear inverse relationship between age and the probability of CLNM, with younger patients exhibiting significantly higher metastasis rates.[14] For these reasons, we chose to retain the 45-years old age cutoff in our analysis. However, due

to the limited representation of older patients in TOETVA, future studies with a broader demographic range are warranted to clarify this issue.

Similarly, the presence of thyroiditis was not significantly associated with oCLNM (OR = 0.97, 95% CI: 0.45 – 2.08, p = 0.94) in our study. This finding suggests that thyroiditis does not independently increase or decrease the likelihood of lymph node metastasis in patients with cN0 PTC undergoing TOETVA. The role of chronic lymphocytic thyroiditis in the progression and metastatic behavior of papillary thyroid carcinoma remains a subject of ongoing debate. Previous studies have reported conflicting results regarding the relationship between thyroiditis and oCLNM. Some research indicates that patients with thyroiditis have a lower risk of oCLNM, possibly due to an enhanced immune-mediated anti-tumor response that restricts tumor progression.[19] However, other studies suggest that chronic inflammation in thyroiditis may promote lymphatic proliferation, facilitating lymph node metastasis and increasing the overall risk of nodal involvemen.[20]

The high prevalence of occult cervical lymph node metastasis in clinically node-negative differentiated thyroid cancer (cN0 DTC) has important implications for surgical management and risk stratification. Our findings support a proactive surgical approach, advocating prophylactic central neck dissection (CND), particularly in patients with identifiable risk factors such as multifocal tumors or primary lesions > 5.5mm. In the context of TOETVA, surgeons may opt for a comprehensive central compartment dissection during the initial operation when preoperative assessment suggests a high likelihood of hidden nodal disease. Removing occult metastases at the time of thyroidectomy can improve initial staging and guide adjuvant therapy decisions – for example, prompting the use of radioiodine ablation in patients found to have node-positive disease. This tailored approach aligns with the principle of individualized surgery: patients with high-risk features for oCLNM could benefit from prophylactic dissection to prevent recurrence.[21] Current guidelines (ATA 2015) give only a weak recommendation for prophylactic central neck dissection in small (T1/T2) node-negative PTC, generally reserving it for advanced primary tumors (T3/T4), clinically evident lateral nodes, or when it will influence adjuvant planning.[22] However, our data suggest that certain "intermediate" risk features – like multifocality – merit consideration alongside traditional high-risk factors (e.g. extrathyroidal extension, aggressive histology or BRAF^V600E mutation) when deciding on the extent of initial surgery. Incorporating these predictors into preoperative risk assessment could refine patient selection for prophylactic central neck dissection beyond the broad guidelines, thereby balancing oncologic benefit against surgical risk.[23] Those with multifocal or larger tumors (even within the T1 category) could be managed more aggressively (e.g. including central node dissection or even upfront total thyroidectomy if bilateral foci are present), whereas solitary small tumors in older patients might be adequately treated with a conservative approach. Our results can inform surgeons employing TOETVA that, when indicated, central neck dissection can be safely and effectively accomplished endoscopically, achieving lymph node yields on par with open surgery.[24] This expands the utility of TOETVA from a purely cosmetic thyroidectomy to a clinically effective procedure capable of managing central cervical lymph node metastasis.

V. CONCLUSION

Occult central lymph node metastasis was present in 41.3% of cases. Among the clinicopathological characteristics analyzed, tumor size > 5.5mm and multifocality were identified as significant independent predictors of oCLNM.

Acknowledgments

The authors would like to express their sincere gratitude to the Board of Directors and all staff members of the Cancer Center – Hanoi Medical University Hospital for their support during data collection and study implementation. We also appreciate all the patients who participated in this study for their valuable cooperation.

Conflict of interest statement

The authors declare that there are no conflicts of interest related to this study.

REFFERENCES

1. Chen DW, Lang BHH, McLeod DSA, et al. Thyroid cancer. *The Lancet*. 2023;401(10387):1531-1544. doi:10.1016/S0140-6736(23)00020-X

2. Hafez LG, Elkomos BE, El-Shafaei MAM, et al. The risk of central nodal metastasis based on prognostic factors of the differentiated thyroid carcinoma: a systematic review and meta-analysis study. *Eur Arch Otorhinolaryngol*. 2023;280(6):2675-2686. doi:10.1007/s00405-023-07863-8

3. Sun W, Lan X, Zhang H, et al. Risk Factors for Central Lymph Node Metastasis in CN0 Papillary Thyroid Carcinoma: A Systematic Review and Meta-Analysis. *PLoS One*. 2015;10(10):e0139021. doi:10.1371/journal.pone.0139021

4. Wen X, Jin Q, Cen X, et al. Clinicopathologic predictors of central lymph node metastases in clinical node-negative papillary thyroid microcarcinoma: a systematic review and meta-analysis. *World Journal of Surgical Oncology*. 2022;20(1):106. doi:10.1186/s12957-022-02573-7

5. Tang L, Qu RW, Park J, et al. Prevalence of Occult Central Lymph Node Metastasis by Tumor Size in Papillary Thyroid Carcinoma: A Systematic Review and Meta-Analysis. *Curr Oncol*. 2023;30(8):7335-7350. doi:10.3390/curroncol30080532

6. Nguyen HX, Nguyen HX, Nguyen TTP, et al. Transoral endoscopic thyroidectomy by vestibular approach in Viet Nam: surgical outcomes and long-term follow-up. *Surg Endosc*. 2022;36(6):4248-4254. doi:10.1007/s00464-021-08759-6

7. Xuan HN, Anh TD, Xuan HN, et al. Occult Central Lymph Node Metastasis in cN0 Papillary Thyroid Carcinoma Patients Undergoing TOETVA Procedure. *J Thyroid Res*. 2023;2023:4779409. doi:10.1155/2023/4779409

8. Nguyen HX, Nguyen HX, Nguyen HV, et al. Transoral Endoscopic Thyroidectomy by Vestibular Approach with Central Lymph Node Dissection for Thyroid Microcarcinoma. *Journal of Laparoendoscopic & Advanced Surgical Techniques*. 2021;31(4):410-415. doi:10.1089/lap.2020.0411

9. Nguyen Xuan Hau, Nguyen Xuan Hien, Hoang Thi Hoai, et al. Quality of Life and Surgical Outcome of Transoral Endoscopic Thyroidectomy Vestibular Approach (TOETVA) versus Open Thyroid Surgery: Experience from a Single Center in Vietnam. *Journal of Thyroid Research*. 2022 Oct 11;2022:2381063.

10. Kwon O, Lee S, Bae JS. The role of prophylactic central compartment neck dissection in patients with T1–T2 cN0 papillary thyroid carcinoma. *Gland Surg*. 2023;12(3):344-

353. doi:10.21037/gs-22-550

11. Xiang Y, Lin K, Dong S, et al. Prediction of central lymph node metastasis in 392 patients with cervical lymph node-negative papillary thyroid carcinoma in Eastern China. *Oncology Letters*. 2015;10(4):2559-2564. doi:10.3892/ol.2015.3544

12. Wu X, Li B, Zheng C, et al. Predicting factors of central lymph node metastases in patients with unilateral multifocal papillary thyroid microcarcinoma. *Gland Surgery*. 2020;9(3):69501-69701. doi:10.21037/gs.2020.03.27

13. Huang Y, Yin Y, Zhou W. Risk Factors for Central and Lateral Lymph Node Metastases in Patients With Papillary Thyroid Micro-Carcinoma: Retrospective Analysis on 484 Cases. *Front Endocrinol (Lausanne)*. 2021;12:640565. doi:10.3389/fendo.2021.640565

14. Kayhan Y, Azizova L, Yılmaz M, et al. Prognostic factors for aggressiveness in subcentimeter papillary thyroid carcinoma: impact of tumor size and lymph node metastases. *Arch Endocrinol Metab*. 2024;68:e230422. doi:10.20945/2359-4292-2023-0422

15. Zhang L, Wei W jun, Ji Q hai, et al. Risk Factors for Neck Nodal Metastasis in Papillary Thyroid Microcarcinoma: A Study of 1066 Patients. *The Journal of Clinical Endocrinology & Metabolism*. 2012;97(4):1250-1257. doi:10.1210/jc.2011-1546

16. Nixon IJ, Kuk D, Wreesmann V, et al. Defining a Valid Age Cutoff in Staging of Well-Differentiated Thyroid Cancer. *Ann Surg Oncol*. 2016;23(2):410-415. doi:10.1245/s10434-015-4762-2

17. Liang-Sen Liu, Jia Liang, Jun-Hong Li, et al. The incidence and risk factors for central lymph node metastasis in cN0 papillary thyroid microcarcinoma: a meta-analysis. *European Archives of Oto-Rhino-Laryngology*. 2017;274:1327-1338.

18. Adam MA, Pura J, Goffredo P, 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. *JCO*. 2015;33(21):2370-2375. doi:10.1200/JCO.2014.59.8391

19. Lai X, Xia Y, Zhang B, et al. A meta-analysis of Hashimoto's thyroiditis and papillary thyroid carcinoma risk. *Oncotarget*. 2017;8(37):62414-62424. doi:10.18632/oncotarget.18620

20. Song E, Jeon MJ, Park S, et al. Influence of coexistent Hashimoto's thyroiditis on the extent of cervical lymph node dissection and prognosis in papillary thyroid carcinoma. *Clin Endocrinol (Oxf)*. 2018;88(1):123-128. doi:10.1111/cen.13475

21. Yoo HS, Shin MC, Ji YB, et al. Optimal extent of prophylactic central neck dissection for papillary thyroid carcinoma: Comparison of unilateral versus bilateral central neck dissection. *Asian J Surg*. 2018;41(4):363-369. doi:10.1016/j.asjsur.2017.03.002

22. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid*. 2017;27(3):315-389. doi:10.1089/thy.2016.0457

23. Matthew L White, Paul G Gauger, Gerard M Doherty. Central Lymph Node Dissection in Differentiated Thyroid Cancer. *World Journal of Surgery*. 2007;31:895-904.

24. Liu Z, Li Y, Wang Y, et al. Comparison of the transoral endoscopic thyroidectomy vestibular approach and open thyroidectomy: A propensity score-matched analysis of surgical outcomes and safety in the treatment of papillary thyroid carcinoma. *Surgery*. 2021;170(6):1680-1686. doi:10.1016/j.surg.2021.06.032