International Journal of General Medicine Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Preoperative High Level of Circulating Tumor Cells is an Independent Risk Factor for Central Lymph Node Metastasis in Papillary Thyroid Carcinoma with Maximum Lesion Diameter ≤1.0 cm

Ming Yu, Jiaqin Deng, Yihua Gu, Yeqian Lai

Department of Thyroid Surgery, Meizhou People's Hospital, Meizhou Academy of Medical Sciences, Meizhou, People's Republic of China

Correspondence: Ming Yu, Department of Thyroid Surgery, Meizhou People's Hospital, Meizhou, People's Republic of China, Email 13543234215@163.com

Objective: Circulating tumor cell (CTC) has been used to assist in the diagnosis and progression assessment of solid tumors, but the relationship between preoperative CTCs levels and central lymph node metastasis (CLNM) of papillary thyroid carcinoma (PTC) needs to be clarified.

Methods: Data on clinical features (age, gender, Hashimoto's thyroiditis, multifocal, maximum lesion diameter, invaded capsule, clinical stage, and status of lymph node metastasis) of PTC patients treated at our hospital between June 2021 and April 2023 were retrospectively collected. The relationship between the CTCs level and these clinical features was analyzed, especially the relationship between the CTCs level and CLNM.

Results: A total of 705 PTC patients were included, and there were 333 (47.2%) patients with CLNM. Patients with a high CTCs level had higher proportions of multifocality, maximum lesion diameter >1cm, and CLNM than those in patients with a low CTCs level. Tumor size was connected to CTCs level, patients with a high CTCs level had a higher proportion of CLNM than those with a low CTCs level in PTC with maximum lesion diameter ≤1cm (45.3% vs 29.7%) (p=0.001). Logistic regression analysis showed that age <55 years old (odds ratio (OR): 2.612, 95% confidence interval (CI): 1.565–4.361, p<0.001), invaded capsule (OR: 1.662, 95% CI: 1.098–2.517, p=0.016), and high CTCs level (≥8.7 FU/3mL, OR: 2.141, 95% CI: 1.431–3.203, p<0.001) were associated with CLNM in PTC with maximum lesion diameter ≤1cm.

Conclusion: In PTC patients with maximum lesion diameter ≤1cm, patients with high preoperative CTCs level (≥ 8.7FU/3mL), age <55 years old, and capsular invasion were prone to CLNM. However, similar results were not observed in patients with maximum lesion diameter >1cm.

Keywords: papillary thyroid carcinoma, circulating tumor cell, central lymph node metastasis, lymph node metastasis

Introduction

Thyroid carcinoma is one of the most common malignancies of the endocrine system with increasing incidence.[1,2] The global cancer statistics in 2020 showed that there were 586,000 new cases, ranking ninth in the global incidence of cancer, and the incidence of women is about 3 times that of men.[3] According to the statistics of the National Cancer Center of China in 2022, thyroid cancer ranking 7th in the incidence of cancer in China.[4] Papillary thyroid cancer (PTC) is one of the least aggressive types of thyroid cancer and rarely develops distant metastases. However, compared with other types of thyroid cancer, PTC has a higher proportion of lymph node metastasis.[5–8] The process of lymph node metastasis (LNM) in PTC is generally from the central lymph node to the lateral cervical lymph node, and a few patients have skip lymph node metastasis.[9] The central cervical region is the most common lymph node metastasis site for PTC, and the incidence of central lymph node metastasis (CLNM) is about 30%-90%, but the preoperative detection rate is low.[10,11]

Received: 21 July 2024
Accepted: 18 October 2024
Published: 25 October 2024

LNM is an important factor affecting the prognosis of PTC, it is very important to evaluate LNM, especially CLNM, in PTC patients.[12] There is no doubt that therapeutic lymph node dissection should be performed in patients with high suspicion and certainty of CLNM, but more researches are needed to provide guidance to clinicians on whether patients with negative lymph node metastases should undergo prophylactic central lymph node dissection.[13–15] Ultrasound and computed tomography (CT) are the methods for screening thyroid nodules and evaluating cervical lymph nodes, but the sensitivity of these methods is disputed.[10,16] On the other hand, ultrasonography (US)-guided fine needle aspiration cytology (UG-FNAC) provides fewer cells for pathological examination and can only observe cell changes, which cannot fully reflect the overall situation of tissue structure.[17,18] Therefore, it is of great value to analyze the risk factors of CLNM according to the clinical characteristics of PTC patients, to provide a simple tool for clinicians to predict the CLNM of PTC.

Several factors have been identified as risk factors for CLNM in PTC patients, such as gender, age, body mass index (BMI), tumor size, multifocality, and *B-Raf proto-oncogene (BRAF)* V600E mutation.[19–22] Circulating tumor cell (CTC) is a type of tumor cell released by tumor tissue into the peripheral blood spontaneously or by the primary site or metastasis due to clinical procedures.[23] At present, CTC has been widely used for early screening, disease monitoring, and prognosis assessment of solid tumors, especially breast cancer,[24] lung cancer,[25] and colorectal cancer.[26] Several studies have found that CTCs are associated with the clinical stage,[27] and prognosis[28,29] of thyroid cancer. High CTCs levels are associated with distant metastasis in differentiated thyroid cancer (DTC) patients.[28] Due to the convenient sample source of CTCs detection, and the fact that CTCs detection can provide a lot of information for the clinical management of PTC patients, the role of CTC in the individualized diagnosis and treatment of thyroid cancer is becoming more and more obvious. However, the relationship between CTCs level and clinicopathological features of PTC patients remains unclear. The aim of this study was to investigate the relationship between the CTCs level and the clinical features, especially the relationship between the CTCs level and CLNM.

Materials and Methods

Subjects

This study retrospectively analyzed 705 patients with PTC who were admitted to Meizhou People's Hospital from June 2021 to April 2023. Inclusion criteria: (1) thyroid surgery was performed and PTC was diagnosed by pathologic examination; (2) the patient's medical records are complete; (3) patients with thyroid cancer as the primary tumor and no co-existing tumors of other types. Exclusion criteria: (1) patients with other thyroid malignancies, or a history of thyroid surgery, and neck irradiation; (2) patients with malignant tumors of other sites; (3) thyroid cancer patients with pathologic types other than PTC. This study was supported by the Ethics Committee of the Meizhou People's Hospital.

Data Collection

The clinicopathological features of the patients collected, such as basic demographic information (age and gender), preoperative circulating tumor cells (CTCs), and pathological data (Hashimoto's thyroiditis, multifocal, maximum lesion diameter, invaded capsule, clinical stage, and status of lymph node metastasis). Patients were divided into age groups of <55 years old and ≥55 years old. According to the size of the tumor diameter, the patients were divided into papillary thyroid microcarcinoma (PTMC) (maximum lesion diameter ≤1cm) and PTC with maximum lesion diameter >1cm.[30,31] According to whether or not the patients had LNM, they were divided into two groups: the patients with LNM and the patients without LNM (including CLNM and lateral cervical lymph node metastasis).[32,33]

Peripheral blood CTCs were enriched and quantified using the CytoploRare Kit according to product manuals (Genosaber Biotech, Shanghai, China) based on reverse transcription-polymerase chain reaction (RT-PCR) technique. CTCs ≥8.7 FU/3mL is the threshold in the instructions of the CTC test kit, and CTCs ≥8.7 FU/3mL (folate receptor-positive CTCs unit in 3mL blood) is interpreted as CTC-positive in this study.

Statistical Analysis

SPSS statistical software (version 26.0, IBM Inc., USA) was used for data analysis. Chi-square test or Fisher's exact test were used to evaluate the relationship between different CTCs levels and clinicopathological features of PTC patients.

Since tumor size was connected to CTCs level,[34] the relationship between CTCs levels and clinicopathological features in patients with different tumor sizes were also analyzed. Univariate analysis and multivariate logistic regression analysis were used to evaluate the relationship between the clinicopathological features and CLNM in PTC patients with maximum lesion diameter ≤1cm. $p<0.05$ was set as statistically significant.

Results

Clinicopathological Features of PTC Patients

Among the 705 patients with PTC, 134 (19.0%) were male patients, 571 (81.0%) were female patients, and 546 (77.4%) cases aged <55 years, and 159 (22.6%) cases aged ≥55 years. There were 394 (55.9%) PTC patients with preoperative CTC-positive, and 311 (44.1%) patients with CTC <8.7 FU/3mL. There were 190 (27.0%), 231 (32.8%), 249 (35.3%), and 326 (46.2%) patients with Hashimoto's thyroiditis, multifocal, maximum lesion diameter >1cm, and invaded capsule, respectively. There were 333 (47.2%) patients with CLNM and 103 (14.6%) patients with lateral cervical lymph node metastasis (Table 1).

Table 1 The Clinicopathological Features of PTC Patients

Clinicopathological Features	PTC Patients (n=705)
Gender	
Male, n (%)	134 (19.0%)
Female, n (%)	571 (81.0%)
Age (Years)	
<55, n (%)	546 (77.4%)
≥55, n (%)	159 (22.6%)
Hashimoto's thyroiditis	
No, n (%)	515 (73.0%)
Yes, n (%)	190 (27.0%)
Multifocal	
No, n (%)	474 (67.2%)
Yes, n (%)	231 (32.8%)
Maximum lesion diameter	
≤1cm, n (%)	456 (64.7%)
>1cm, n (%)	249 (35.3%)
Invaded capsule	
No, n (%)	379 (53.8%)
Yes, n (%)	326 (46.2%)
T stage	
T1-T2, n (%)	639 (90.6%)
T3-T4, n (%)	66 (9.4%)
Central lymph node metastasis	
No, n (%)	372 (52.8%)
Yes, n (%)	333 (47.2%)
Lateral cervical lymph node metastasis	
No, n (%)	602 (85.4%)
Yes, n (%)	103 (14.6%)
Preoperative circulating tumor cells (CTCs) (FU/3mL)	
<8.7	311 (44.1%)
≥8.7	394 (55.9%)

Abbreviations: PTC, papillary thyroid carcinoma; CTC, circulating tumor cell; FU, folate receptor unit.

Comparison of Clinicopathological Features Among PTC Patients with CTCs Negative or Positive

Compared with patients with CTCs <8.7 FU/3mL, PTC patients with CTCs ≥8.7 FU/3mL had a higher proportion of multifocality (36.3% vs 28.3%) (p=0.029), and maximum lesion diameter >1cm (40.6% vs 28.6%) (p=0.001), and CLNM (52.5% vs 40.5%) (p=0.002). There was no statistically significant difference in distributions of gender and age, and proportions of Hashimoto's thyroiditis, invaded capsule, T stage, and lateral cervical lymph node metastasis between patients with different CTCs levels (Table 2).

Comparison of Clinicopathological Features of Different CTCs Levels Among PTC Patients with Maximum Lesion Diameter ≤1cm, and Maximum Lesion Diameter >1cm, Respectively

In PTC patients with maximum lesion diameter ≤1cm, patients with CTCs ≥8.7 FU/3mL had a higher proportion of CLNM (45.3% vs 29.7%) (p=0.001) than that in patients with CTCs <8.7 FU/3mL. No difference in other clinicopathological features were found between different CTCs levels. In PTC patients with maximum lesion diameter >1cm, no clinicopathological features associated with CTCs level were found (Table 3).

Table 2 Comparison of Clinicopathological Features Among PTC Patients with CTCs Negative or Positive

Clinicopathological Features	CTCs (FU/3mL)		*p* values
	<8.7 (n=311)	≥8.7 (n=394)	
Gender			
Male, n (%)	56(18.0%)	78(19.8%)	0.563
Female, n (%)	255(82.0%)	316(80.2%)	
Age (Years)			
<55, n (%)	242(77.8%)	304(77.2%)	0.856
≥55, n (%)	69(22.2%)	90(22.8%)	
Hashimoto's thyroiditis			
No, n (%)	235(75.6%)	280(71.1%)	0.200
Yes, n (%)	76(24.4%)	114(28.9%)	
Multifocal			
No, n (%)	223(71.7%)	251(63.7%)	0.029
Yes, n (%)	88(28.3%)	143(36.3%)	
Maximum lesion diameter			
≤1cm, n (%)	222(71.4%)	234(59.4%)	0.001
>1cm, n (%)	89(28.6%)	160(40.6%)	
Invaded capsule			
No, n (%)	169(54.3%)	210(53.3%)	0.820
Yes, n (%)	142(45.7%)	184(46.7%)	
T stage			
T1-T2, n (%)	283(91.0%)	356(90.4%)	0.796
T3-T4, n (%)	28(9.0%)	38(9.6%)	
Central lymph node metastasis			
No, n (%)	185(59.5%)	187(47.5%)	0.002
Yes, n (%)	126(40.5%)	207(52.5%)	
Lateral cervical lymph node metastasis			
No, n (%)	269(86.5%)	333(84.5%)	0.520
Yes, n (%)	42(13.5%)	61(15.5%)	

Abbreviations: PTC, papillary thyroid carcinoma; CTC, circulating tumor cell; FU, folate receptor unit.

Table 3 Comparison of Clinicopathological Features of Different CTCs Levels Among PTC Patients with Maximum Lesion Diameter ≤1cm, and Maximum Lesion Diameter >1cm, Respectively

Clinicopathological Features	Maximum Lesion Diameter					
	≤1cm			>1cm		
	CTCs<8.7 (n=222)	CTCs≥8.7 (n=234)	*p* values	CTCs<8.7 (n=89)	CTCs≥8.7 (n=160)	*p* values
Gender						
Male, n (%)	34(15.3%)	43(18.4%)	0.453	22(24.7%)	35(21.9%)	0.639
Female, n (%)	188(84.7%)	191(81.6%)		67(75.3%)	125(78.1%)	
Age (Years)						
<55, n (%)	176(79.3%)	172(73.5%)	0.154	66(74.2%)	132(82.5%)	0.141
≥55, n (%)	46(20.7%)	62(26.5%)		23(25.8%)	28(17.5%)	
Hashimoto's thyroiditis						
No, n (%)	173(77.9%)	165(70.5%)	0.087	62(69.7%)	115(71.9%)	0.771
Yes, n (%)	49(22.1%)	69(29.5%)		27(30.3%)	45(28.1%)	
Invaded capsule						
No, n (%)	140(63.1%)	148(63.2%)	1.000	29(32.6%)	62(38.8%)	0.341
Yes, n (%)	82(36.9%)	86(36.8%)		60(67.4%)	98(61.3%)	
T stage						
T1-T2, n (%)	217(97.7%)	229(97.9%)	1.000	66(74.2%)	127(79.4%)	0.429
T3-T4, n (%)	5(2.3%)	5(2.1%)		23(25.8%)	33(20.6%)	
Central lymph node metastasis						
No, n (%)	156(70.3%)	128(54.7%)	0.001	29(32.6%)	59(36.9%)	0.580
Yes, n (%)	66(29.7%)	106(45.3%)		60(67.4%)	101(63.1%)	
Lateral cervical lymph node metastasis						
No, n (%)	211(95.0%)	217(92.7%)	0.335	58(65.2%)	116(72.5%)	0.250
Yes, n (%)	11(5.0%)	17(7.3%)		31(34.8%)	44(27.5%)	

Abbreviations: PTC, papillary thyroid carcinoma; CTC, circulating tumor cell.

Logistic Regression Analysis of Risk Factors of CLNM in PTC with Maximum Lesion Diameter ≤1cm

Age <55 years old (odds ratio (OR): 2.428, 95% confidence interval (CI): 1.480–3.984, $p<0.001$), invaded capsule (OR: 1.719, 95% CI: 1.163–2.540, $p=0.007$), and high preoperative CTCs level (≥8.7/<8.7 FU/3mL, OR: 1.957, 95% CI: 1.330–2.880, $p=0.001$) were found significantly associated with CLNM in PTC with maximum lesion diameter ≤1cm by univariate analysis. And age <55 years old (OR: 2.612, 95% CI: 1.565–4.361, $p<0.001$), invaded capsule (OR: 1.662, 95% CI: 1.098–2.517, $p=0.016$), and high preoperative CTCs level (≥8.7/<8.7 FU/3mL, OR: 2.141, 95% CI: 1.431–3.203, $p<0.001$) were independently associated with CLNM in PTC with maximum lesion diameter ≤1cm showed in multivariate regression logistic analysis (Table 4).

Discussion

Thyroid cancer is mainly diagnosed by UG-FNAC and is classified according to the cell of origin.[35,36] Although UG-FNAC is the gold standard for thyroid cancer diagnosis, there are still some inaccuracies.[37] PTC is an inert cancer with good prognosis, but it has a high probability of cervical LNM.[38] At present, thyroid surgery is one of the effective treatment methods for thyroid cancer, but there are still inconsistent views on the scope of lymph node dissection during surgery.[39,40] Comprehensive regional lymph node dissection may reduce the recurrence rate, but excessive lymph node dissection may increase the risk of recurrent laryngeal nerve injury.[41–43] Preoperative prediction and evaluation of lymph node metastasis of thyroid cancer can provide basis for the selection of surgical methods. In recent years, non-invasive liquid biopsy has attracted much attention, and the detection of circulating tumor markers based on CTCs has important clinical value.[44,45]

Table 4 Logistic Regression Analysis of Risk Factors of CLNM in PTC with Maximum Lesion Diameter ≤1cm

Variables	Univariate		Multivariate	
	OR (95% CI)	*p* values	OR (95% CI)	*p* values
Gender (Male/Female)	1.381 (0.841–2.268)	0.202	1.239 (0.735–2.089)	0.421
Age (<55/≥55, years old)	2.428 (1.480–3.984)	<0.001	2.612 (1.565–4.361)	<0.001
Hashimoto's thyroiditis (Yes/No)	0.841 (0.543–1.303)	0.439	0.775 (0.490–1.228)	0.278
Multifocal (Yes/No)	1.392 (0.923–2.100)	0.114	1.145 (0.739–1.773)	0.544
T stage (T3-T4/T1-T2)	1.671 (0.477–5.857)	0.423	1.522 (0.396–5.847)	0.541
Invaded capsule (Yes/No)	1.719 (1.163–2.540)	0.007	1.662 (1.098–2.517)	0.016
Preoperative CTCs (≥8.7/<8.7, FU/3mL)	1.957 (1.330–2.880)	0.001	2.141 (1.431–3.203)	<0.001

Abbreviations: CLNM, central lymph node metastasis; PTC, papillary thyroid carcinoma; CTC, circulating tumor cell; FU, folate receptor unit; OR, odds ratio; CI, confidence interval.

Since Ringel et al confirmed the existence of CTCs in peripheral blood of patients with recurrent and distant metastatic thyroid cancer in 1998,[46] more and more studies have begun to pay attention to the application value of CTCs in thyroid cancer. The results of a prospective study by Xu et al showed that CTCs were effective diagnostic markers for thyroid nodules.[47] The findings of some studies suggested that high CTCs levels were associated with worse overall survival (OS),[29] and shorter progression-free survival (PFS)[48] in patients with thyroid cancer. Liang et al found that CTC was a reliable index for the diagnosis of thyroid cancer with recurrence and distant metastasis.[49] Regarding the role of CTCs in LNM in PTC patients, Zeng et al found that there was significant difference in the number of CTCs between N0 and N1 patients with thyroid cancer.[50] The results of this study also suggested that high preoperative CTCs level (≥8.7/FU/3mL) was an independent risk factor for CLNM in PTC with maximum lesion diameter ≤1cm. At present, most studies have shown that CTCs detection can provide some useful information for the diagnosis, treatment, and monitoring of thyroid cancer, but its role in the individualized diagnosis and treatment of thyroid cancer is still unable to be evaluated.[51] In addition, different analysis methods for CTCs may produce different results. At present, there is a lack of recognized CTCs detection methods with high sensitivity and specificity.[52,53] Therefore, further improvement of CTCs detection technology and effective isolation of single CTC for molecular characterization analysis will be of great significance for its clinical application in thyroid cancer.

Regarding the role of age in LNM of thyroid cancer, a study showed that there was a higher risk of LNM in older patients with PTC.[54] However, Mao et al showed that younger patients with PTC have a higher risk of LNM.[55] Similarly, Zhang et al showed that the proportion of LNM in older patients with PTC was relatively small.[56] Some studies have also shown that age was significantly correlated with CLNM.[57–60] The results of this study also suggested that age is an independent risk factor for CLNM, with PTC patients aged <55 years old having a greater risk of CLNM than patients ≥55 years of age. Study suggested that the relationship between age difference and disease severity may be related to differentially expressed genes, such as low expression of extracellular matrix protein 1 (ECM1),[61] but its role in tumorigenesis has not been fully elucidated.

Thyroid cancer is more prevalent in women adults.[62] Several studies have shown that estrogen is a powerful stimulating factor for benign and malignant thyroid nodules, and circulating estrogen increases women's susceptibility to thyroid proliferative diseases and tumor transformation, which is one of the reasons why thyroid cancer is more common in women.[63,64] In addition, several studies have reported that CLNM is more likely to occur in male patients with PTC, and PTC is more aggressive and has worse prognosis in males.[20,59,60,65] This study did not find a relationship between gender and CLNM. Moreover, some studies also showed that without Hashimoto's thyroiditis,[59,66,67] and multifocal,[59,60,68–70] and invasion capsule[71,72] were independent risk predictors of CLNM in papillary thyroid micro-carcinoma (PTMC). But this study did not get the same results.

In this study, age <55 years old, invaded capsule, and high preoperative CTCs level (≥8.7 FU/3mL) were independent risk factors for CLNM in PTC with maximum lesion diameter ≤1cm. Prophylactic central lymph node dissection in PTMC remains controversial,[59,73] it is necessary to combine factors such as age, capsule invasion, and CTC level, rather

than fixed surgical methods, to obtain greater benefits of individualized treatment. The results of this study provide meaningful information for the risk assessment of CLNM in PTC with maximum lesion diameter ≤1cm. Of course, this study inevitably has some shortcomings that need to be improved. First of all, as this study is a single-center retrospective study, the possibility of case selection bias resulting in results bias cannot be ruled out. Secondly, patients with PTC who are in remission may still experience an increase in the number of CTCs,[27] so the assessment of CTC levels on the progression of PTC patients still needs to be confirmed by more studies. In addition, to demonstrate the clinical value of CTCs in evaluating lymph node metastasis of thyroid cancer, more cases need to be collected for validation, so multi-center studies are needed in the future to further investigate the risk factors and clinical interventions for CLNM of thyroid cancer.

Conclusions

High preoperative CTCs level (≥8.7 FU/3mL), age <55 years old, and invaded capsule were independent risk factors for CLNM in PTC with maximum lesion diameter ≤1cm. In other words, in PTC patients with maximum lesion diameter ≤1cm, patients with high preoperative CTCs level (≥ 8.7FU/3mL), age <55 years old, and capsular invasion were prone to CLNM. Whereas there was no relationship between the levels of CTCs and LNM in patients with PTC whose tumor size was >1 cm. It provides valuable reference data for the risk assessment of CLNM in PTC.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

All participants were informed on the study procedures and goals and the informed consent from all the participants was obtained. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital.

Acknowledgments

The author would like to thank other colleagues whom were not listed in the authorship of Department of Thyroid Surgery, Meizhou People's Hospital for their helpful comments on the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Scientific Research Cultivation Project of Meizhou People's Hospital (Grant No.: PY-C2023046).

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Houten PV, Netea-Maier RT, Smit JW. Differentiated thyroid carcinoma: an update. *Best Pract Res Clin Endocrinol Metab*. 2023;37(1):101687. doi:10.1016/j.beem.2022.101687
2. Yan K, Liu QZ, Huang RR, et al. Spatial transcriptomics reveals prognosis-associated cellular heterogeneity in the papillary thyroid carcinoma microenvironment. *Clin Transl Med*. 2024;14(3):e1594. doi:10.1002/ctm2.1594
3. Sung H, Ferlay J, Siegel RL. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660

4. Wang Y, Yan Q, Fan C, et al. Overview and countermeasures of cancer burden in China. *Sci China Life Sci*. 2023;66(11):2515–2526. doi:10.1007/s11427-022-2240-6
5. Feng Y, Min Y, Chen H, Xiang K, Wang X, Yin G. Construction and validation of a nomogram for predicting cervical lymph node metastasis in classic papillary thyroid carcinoma. *J Endocrinol Invest*. 2021;44(10):2203–2211. doi:10.1007/s40618-021-01524-5
6. Li T, Li H, Xue J, Miao J, Kang C. Shear wave elastography combined with gray-scale ultrasound for predicting central lymph node metastasis of papillary thyroid carcinoma. *Surg Oncol*. 2021;36:1–6. doi:10.1016/j.suronc.2020.11.004
7. Zhang TT, Qi XZ, Chen JP, et al. The association between tumor's location and cervical lymph nodes metastasis in papillary thyroid cancer. *Gland Surg*. 2019;8(5):557–568. doi:10.21037/gs.2019.10.02
8. Alabousi M, Alabousi A, Adham S, et al. Diagnostic test accuracy of ultrasonography vs computed tomography for papillary thyroid cancer cervical lymph node metastasis: a systematic review and meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2022;148(2):107–118. doi:10.1001/jamaoto.2021.3387
9. Seok J, Ryu CH, Park SY, et al. Factors affecting central node metastasis and metastatic lymph node ratio in papillary thyroid cancer. *Otolaryngol Head Neck Surg*. 2021;165(4):519–527. doi:10.1177/0194599821991465
10. Li F, Pan D, He Y, et al. Using ultrasound features and radiomics analysis to predict lymph node metastasis in patients with thyroid cancer. *BMC Surg*. 2020;20(1):315. doi:10.1186/s12893-020-00974-7
11. Tan L, Ji J, Sharen G, Liu Y, Lv K. Related factor analysis for predicting large-volume central cervical lymph node metastasis in papillary thyroid carcinoma. *Front Endocrinol*. 2022;13:935559. doi:10.3389/fendo.2022.935559
12. Zhang J, Fu C, Cui K, Ma X. Papillary thyroid carcinoma with tracheal invasion: a case report. *Medicine*. 2019;98(38):e17033. doi:10.1097/MD.0000000000017033
13. Zhong X, Lu Y, Yin X, Wang Q, Wang F, He Z. Prophylactic central lymph node dissection performed selectively with cN0 papillary thyroid carcinoma according to a risk-scoring model. *Gland Surg*. 2022;11(2):378–388. doi:10.21037/gs-21-906
14. Nylén C, Eriksson FB, Yang A, et al. Prophylactic central lymph node dissection informs the decision of radioactive iodine ablation in papillary thyroid cancer. *Am J Surg*. 2021;221(5):886–892. doi:10.1016/j.amjsurg.2020.08.012
15. Alsubaie KM, Alsubaie HM. Prophylactic central neck dissection for clinically node-negative papillary thyroid carcinoma. *Laryngoscope*. 2022;132(6):1320–1328. doi:10.1002/lary.29912
16. Wang Y, Duan Y, Zhou M, et al. The diagnostic value of thyroglobulin in fine-needle aspiration of metastatic lymph nodes in patients with papillary thyroid cancer and its influential factors. *Surg Oncol*. 2021;39:101666. doi:10.1016/j.suronc.2021.101666
17. Jiang HJ, Wu CW, Chiang FY, Chiou HY, Chen IJ, Hsiao PJ. Reliable sonographic features for nodal thyroglobulin to diagnose recurrent lymph node metastasis from papillary thyroid carcinoma. *Clin Otolaryngol*. 2018;43(4):1065–1072. doi:10.1111/coa.13103
18. Khadra H, Mohamed H, Al-Qurayshi Z, Sholl A, Killackey M, Kandil E. Superior detection of metastatic cystic lymphadenopathy in patients with papillary thyroid cancer by utilization of thyroglobulin washout. *Head Neck*. 2019;41(1):225–229. doi:10.1002/hed.25488
19. Du J, Yang Q, Sun Y, et al. Risk factors for central lymph node metastasis in patients with papillary thyroid carcinoma: a retrospective study. *Front Endocrinol*. 2023;14:1288527. doi:10.3389/fendo.2023.1288527
20. Yan B, Hou Y, Chen D, He J, Jiang Y. Risk factors for contralateral central lymph node metastasis in unilateral cN0 papillary thyroid carcinoma: a meta-analysis. *Int J Surg*. 2018;59:90–98. doi:10.1016/j.ijsu.2018.09.004
21. Li X, Zhang H, Zhou Y, Cheng R. Risk factors for central lymph node metastasis in the cervical region in papillary thyroid carcinoma: a retrospective study. *World J Surg Oncol*. 2021;19(1):138. doi:10.1186/s12957-021-02247-w
22. Zhao YZ, He NA, Ye XJ, Jin F, Li MX, Jiang X. Analysis of risk factors associated with central lymph node metastasis in papillary thyroid carcinoma with cT1N0 stage. *Front Endocrinol*. 2022;13:880911. doi:10.3389/fendo.2022.880911
23. Lin D, Shen L, Luo M, et al. Circulating tumor cells: biology and clinical significance. *Signal Transduct Target Ther*. 2021;6(1):404. doi:10.1038/s41392-021-00817-8
24. Alemzadeh E, Allahqoli L, Dehghan H, Mazidimoradi A, Ghasempour A, Salehiniya H. Circulating tumor cells and circulating tumor DNA in breast cancer diagnosis and monitoring. *Oncol Res*. 2023;31(5):667–675. doi:10.32604/or.2023.028406
25. Maly V, Maly O, Kolostova K, Bobek V. Circulating tumor cells in diagnosis and treatment of lung cancer. *In vivo*. 2019;33(4):1027–1037. doi:10.21873/invivo.11571
26. Petrik J, Verbanac D. Circulating tumor cells in colorectal cancer: detection systems and clinical utility. *Int J Mol Sci*. 2022;23(21):13582. doi:10.3390/ijms232113582
27. Ehlers M, Allelein S, Schwarz F, et al. Increased numbers of circulating tumor cells in thyroid cancer patients. *Horm Metab Res*. 2018;50(8):602–608. doi:10.1055/a-0651-4913
28. Qiu ZL, Wei WJ, Sun ZK, et al. Circulating tumor cells correlate with clinicopathological features and outcomes in differentiated thyroid cancer. *Cell Physiol Biochem*. 2018;48(2):718–730. doi:10.1159/000491898
29. Xu JY, Handy B, Michaelis CL, et al. Detection and prognostic significance of circulating tumor cells in patients with metastatic thyroid cancer. *J Clin Endocrinol Metab*. 2016;101(11):4461–4467. doi:10.1210/jc.2016-2567
30. Didehban S, Abdollahi A, Meysamie A. Evaluation of etiology, clinical manifestations, diagnosis, follow-up, histopathology and prognosis factors in papillary thyroid microcarcinoma: a systematic review and meta-analysis. *Iran J Pathol*. 2023;18(4):380–391. doi:10.30699/IJP.2023.2005196.3134
31. Ma T, Semsarian CR, Barratt A, et al. Rethinking low-risk papillary thyroid cancers < 1cm (papillary microcarcinomas): an evidence review for recalibrating diagnostic thresholds and/or alternative labels. *Thyroid*. 2021;31(11):1626–1638. doi:10.1089/thy.2021.0274
32. Luo Y, Zhao Y, Chen K, et al. Clinical analysis of cervical lymph node metastasis risk factors in patients with papillary thyroid microcarcinoma. *J Endocrinol Invest*. 2019;42(2):227–236. doi:10.1007/s40618-018-0908-y
33. Lou J, Yang J, Luo Y, Zhu Y, Xu Z, Hua T. Analysis of the influence factors of cervical lymph node metastasis in papillary thyroid carcinoma: a retrospective observational study. *Medicine*. 2023;102(36):e35045. doi:10.1097/MD.0000000000035045
34. Netterberg I, Karlsson MO, Terstappen L. Comparing circulating tumor cell counts with dynamic tumor size changes as predictor of overall survival: a quantitative modeling framework. *Clin Cancer Res*. 2020;26(18):4892–4900. doi:10.1158/1078-0432.CCR-19-2570
35. Zhuo Y, Fang H, Yuan J, Gong L, Zhang Y. Fine-needle aspiration biopsy evaluation-oriented thyroid carcinoma auxiliary diagnosis. *Ultrasound Med Biol*. 2023;49(5):1173–1181. doi:10.1016/j.ultrasmedbio.2023.01.002

36. Krane JF, Cibas ES, Endo M. The Afirma Xpression Atlas for thyroid nodules and thyroid cancer metastases: insights to inform clinical decision-making from a fine-needle aspiration sample. *Cancer Cytopathol*. 2020;128(7):452–459. doi:10.1002/cncy.22300
37. Abou-Foul AK, Muzaffar J, Diakos E, Best JE, Momtahan N, Jayaram S. Correlation between thyroid fine needle aspiration cytology and postoperative histology: a 10-year single-centre experience. *Cureus*. 2021;13(4):e14504. doi:10.7759/cureus.14504
38. Zhang Q, Li J, Shen H, Bai X, Zhang T, Liu P. Screening and validation of lymph node metastasis risk-factor genes in papillary thyroid carcinoma. *Front Endocrinol*. 2022;13:991906. doi:10.3389/fendo.2022.991906
39. Li Y, Lao L. Comparison of prophylactic ipsilateral and bilateral central lymph node dissection in papillary thyroid carcinoma: a meta-analysis. *Braz J Otorhinolaryngol*. 2023;89(6):101318. doi:10.1016/j.bjorl.2023.101318
40. Aygun N, Kostek M. Role and extent of neck dissection for neck lymph node metastases in differentiated thyroid cancers. *Sisli Etfal Hastan Tip Bul*. 2021;55(4):438–449. doi:10.14744/SEMB.2021.76836
41. Zhao WJ, Luo H, Zhou YM, Dai WY, Zhu JQ. Evaluating the effectiveness of prophylactic central neck dissection with total thyroidectomy for cN0 papillary thyroid carcinoma: an updated meta-analysis. *Eur J Surg Oncol*. 2017;43(11):1989–2000. doi:10.1016/j.ejso.2017.07.008
42. Sterpetti AV. Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma. *Ann Surg*. 2015;261(1):e30. doi:10.1097/SLA.0b013e31824b7b68
43. Su H, Li Y. Prophylactic central neck dissection and local recurrence in papillary thyroid microcarcinoma: a meta-analysis. *Braz J Otorhinolaryngol*. 2019;85(2):237–243. doi:10.1016/j.bjorl.2018.05.004
44. Siravegna G, Marsoni S, Siena S, Bardelli A. Integrating liquid biopsies into the management of cancer. *Nat Rev Clin Oncol*. 2017;14(9):531–548. doi:10.1038/nrclinonc.2017.14
45. Nikanjam M, Kato S, Kurzrock R. Liquid biopsy: current technology and clinical applications. *J Hematol Oncol*. 2022;15(1):131. doi:10.1186/s13045-022-01351-y
46. Ringel MD, Ladenson PW, Levine MA. Molecular diagnosis of residual and recurrent thyroid cancer by amplification of thyroglobulin messenger ribonucleic acid in peripheral blood. *J Clin Endocrinol Metab*. 1998;83(12):4435–4442. doi:10.1210/jcem.83.12.5346
47. Xu S, Cheng J, Wei B, et al. Development and validation of circulating tumor cells signatures for papillary thyroid cancer diagnosis: a prospective, blinded, multicenter study. *Clin Transl Med*. 2020;10(4):e142. doi:10.1002/ctm2.142
48. Weng X, Yang Y, Cai Y. Clinical significance of circulating tumor cells (CTCs) and survivin on predicting prognosis in thyroid cancer patients. *Dis Markers*. 2022;2022:5188006. doi:10.1155/2022/5188006
49. Liang MX, Fei YJ, Yang K, Tang WJ, Cao XH, Tang JH. Potential values of circulating tumor cell for detection of recurrence in patients of thyroid cancer: a diagnostic meta-analysis. *BMC Cancer*. 2022;22(1):954. doi:10.1186/s12885-022-09976-5
50. Zeng Q, Zhong H, Rao H, Wang Y. Diagnostic value of circulating tumor cells in patients with thyroid cancer: a retrospective study of 1478 patients. *Discov Oncol*. 2024;15(1):114. doi:10.1007/s12672-024-00976-4
51. Jin KT, Chen XY, Lan HR, et al. Current progress in the clinical use of circulating tumor cells as prognostic biomarkers. *Cancer Cytopathol*. 2019;127(12):739–749. doi:10.1002/cncy.22189
52. Deng Z, Wu S, Wang Y, Shi D. Circulating tumor cell isolation for cancer diagnosis and prognosis. *EBioMedicine*. 2022;83:104237. doi:10.1016/j.ebiom.2022.104237
53. He S, Wei J, Ding L, Yang X, Wu Y. State-of-the-arts techniques and current evolving approaches in the separation and detection of circulating tumor cell. *Talanta*. 2022;239:123024. doi:10.1016/j.talanta.2021.123024
54. Shukla N, Osazuwa-Peters N, Megwalu UC. Association between age and nodal metastasis in papillary thyroid carcinoma. *Otolaryngol Head Neck Surg*. 2021;165(1):43–49. doi:10.1177/0194599820966995
55. Mao J, Zhang Q, Zhang H, Zheng K, Wang R, Wang G. Risk factors for lymph node metastasis in papillary thyroid carcinoma: a systematic review and meta-analysis. *Front Endocrinol*. 2020;11:265. doi:10.3389/fendo.2020.00265
56. Zhang K, Qian L, Chen J, Zhu Q, Chang C. Preoperative prediction of central cervical lymph node metastasis in fine-needle aspiration reporting suspicious papillary thyroid cancer or papillary thyroid cancer without lateral neck metastasis. *Front Oncol*. 2022;12:712723. doi:10.3389/fonc.2022.712723
57. Wang Z, Chang Q, Zhang H, et al. A clinical predictive model of central lymph node metastases in papillary thyroid carcinoma. *Front Endocrinol*. 2022;13:856278. doi:10.3389/fendo.2022.856278
58. Liu Y, Lv H, Zhang S, Shi B, Sun Y. The impact of coexistent Hashimoto's thyroiditis on central compartment lymph node metastasis in papillary thyroid carcinoma. *Front Endocrinol*. 2021;12:772071. doi:10.3389/fendo.2021.772071
59. Wang D, Hu J, Deng C, Yang Z, Zhu J, Su X. Predictive nomogram for central lymph node metastasis in papillary thyroid microcarcinoma based on pathological and ultrasound features. *Front Endocrinol*. 2023;14:1108125. doi:10.3389/fendo.2023.1108125
60. 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(3):201–207. doi:10.1055/s-0043-101917
61. Vriens MR, Moses W, Weng J, et al. Clinical and molecular features of papillary thyroid cancer in adolescents and young adults. *Cancer*. 2011;117(2):259–267. doi:10.1002/cncr.25369
62. Haymart MR. Progress and challenges in thyroid cancer management. *Endocr Pract*. 2021;27(12):1260–1263. doi:10.1016/j.eprac.2021.09.006
63. Derwahl M, Nicula D. Estrogen and its role in thyroid cancer. *Endocr Relat Cancer*. 2014;21(5):T273–283. doi:10.1530/ERC-14-0053
64. Antico-Arciuch VG, Dima M, Liao XH, Refetoff S, Di Cristofano A. Cross-talk between PI3K and estrogen in the mouse thyroid predisposes to the development of follicular carcinomas with a higher incidence in females. *Oncogene*. 2010;29(42):5678–5686. doi:10.1038/onc.2010.308
65. Pastorčić Grgić M, Stubljar B, Perše P, Zekan Vučetić M, Šitić S. Total thyroidectomy with central node dissection is a valuable option in papillary thyroid cancer treatment. *Acta Clin Croat*. 2020;59(Suppl 1):102–107. doi:10.20471/acc.2020.59.s1.13
66. Huang H, Xu S, Ni S, Liu W, Liu S. Hashimoto's thyroiditis is negatively associated with lymph node metastasis in PTMC. *J Cancer Res Clin Oncol*. 2023;149(17):15525–15533. doi:10.1007/s00432-023-05332-7
67. Ma T, Wang L, Zhang X, Shi Y. A clinical and molecular pathology prediction model for central lymph node metastasis in cN0 papillary thyroid microcarcinoma. *Front Endocrinol*. 2023;14:1075598. doi:10.3389/fendo.2023.1075598
68. Qu N, Zhang L, Ji QH, et al. Risk factors for central compartment lymph node metastasis in papillary thyroid microcarcinoma: a meta-analysis. *World J Surg*. 2015;39(10):2459–2470. doi:10.1007/s00268-015-3108-3

69. Wang D, Zhu J, Deng C, et al. Preoperative and pathological predictive factors of central lymph node metastasis in papillary thyroid microcarcinoma. *Auris Nasus Larynx*. 2022;49(4):690–696. doi:10.1016/j.anl.2021.12.006
70. Sheng L, Shi J, Han B, et al. Predicting factors for central or lateral lymph node metastasis in conventional papillary thyroid microcarcinoma. *Am J Surg*. 2020;220(2):334–340. doi:10.1016/j.amjsurg.2019.11.032
71. Shen Y, Pu W, Zhou H, et al. Risk factors for central lymph node metastasis in papillary thyroid microcarcinoma - a retrospective study of 1433 cases from a single center. *Pol J Pathol*. 2022;73(3):191–197. doi:10.5114/pjp.2022.124486
72. Wang Z, Gui Z, Wang Z. Clinical and ultrasonic risk factors for high-volume central lymph node metastasis in cN0 papillary thyroid microcarcinoma: a retrospective study and meta-analysis. *Clin Endocrinol*. 2023;98(4):609–621. doi:10.1111/cen.14834
73. Liu W, Wang S, Xia X. Risk factor analysis for central lymph node metastasis in papillary thyroid microcarcinoma. *Int J Gen Med*. 2021;14:9923–9929. doi:10.2147/IJGM.S346143