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Original Article

Clinical value of ultrasound parameters PI, TTP, and MTT in assessing cervical lymph node metastasis of papillary thyroid carcinoma

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Abstract: Objective: To determine the clinical value of ultrasound in assessing cervical lymph node metastasis (CLNM) in papillary thyroid carcinoma (PTC). Methods: The medical records of 179 PTC patients treated in Shandong Provincial Qianfoshan Hospital between March 2016 and March 2019 were collected. The patients were assigned to a transfer group (54 cases) and a non-transfer group (125 cases) according to their pathologic results. The ultrasound parameters (peak intensity (PI), time to peak (TTP), and mean transit time (MTT)) of the two groups were compared. Then, multivariate logistic regression was used to analysis the results, and receiver operating characteristic (ROC) curves were plotted to evaluate the value of risk factors in predicting CLNM. Results: The transfer group showed notably lower PI, TTP and MTT than the non-transfer group (P<0.001), and focus diameter, microcalcification, multiple foci, PI, TTP, and MTT were identified as independent risk factors for LNM in patients (P<0.05). According to the ROC curve, the areas under the curves (AUCs) of microcalcification, multiple foci, and PI were all smaller than 0.7; the AUCs of focus diameter and MTT were smaller than 0.8, and the AUC of TTP was 0.855. Conclusion: PI, TTP, and MTT all decrease in PTC patients with CLNM, and TTP has a strong predictor for CLNM in them, with an AUC of 0.855.

Keywords: Ultrasound parameters, papillary thyroid carcinoma, cervical lymph node metastasis, diagnostic value

Introduction

The worldwide incidence of thyroid nodules is on the rise, with papillary carcinoma being the predominant malignant type [1]. The known increase in the thyroid cancer incidence can be largely attributed to the progress of ultrasound examinations and the formal population screening programs [2]. Moreover, covid-19 has led to delays in examinations and treatment, contributing to an increased positive rate of thyroid malignant tumors [3]. Papillary thyroid carcinoma (PTC), the most frequently-seen subtype of malignant thyroid tumors, is characterized by its indolent nature and slow development [4]. Although PTC is generally an indolent tumor, it often exhibits metastasis even when its nodules have no obvious characteristics in the early stage. This is attributed to the rich lymphatic network in the thyroid gland, with 30%-80% of PTC patients experiencing cervical lymph node metastasis (CLNM) [5]. When PTC cells invade cervical lymph nodes, it not only expands the scope and complexity of the operation, but also increases the risk of local tumor recurrence, resulting a requirement of further therapy [6]. Accordingly, early and accurate identification of metastatic lymph nodes can effectively guide clinicians in performing active therapeutic lymph node dissection.

At present, imaging examinations including ultrasound, CT and MRI are crucial means to evaluate the metastasis of lymph nodes before operation [7]. Ultrasound, as a safe and non-invasive imaging technique, is the first choice for thyroid nodule screening [8]. Compared with other examination methods, ultrasound has the

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unique advantages of repeatability, no radiation, and real-time detection of the internal structure and adjacent parts of the focal point [9]. According to prior research, contrast-enhanced ultrasound revealed an incidence of thyroid nodules of about 20%-76% during screening, and a diagnostic rate of PTC of about 5%-15%, and it is becoming the first choice for detection and diagnosis of CLNM in PTC patients [10]. Another study also reported that preoperative ultrasound could help diagnose CLNM in PTC to some extent [11]. In routine ultrasound examinations, tumor size, capsule infiltration, nodular microcalcification, and multiple foci are all important risk factors for CLNM [12].

This study analyzed the clinical value of ultrasound parameters in assessing CLNM in PTC to provide potential indexes for clinical diagnosis and prognosis prediction.

Materials and methods

Clinical data

The medical records of 179 PTC patients treated in Shandong Provincial Qianfoshan Hospital between March 2016 and March 2019 were retrospectively analyzed. The patients were assigned to a transfer group (54 cases) and a non-transfer group (125 cases) according to their pathologic results. This study had ethical approved by the Medical Ethics Committee of Shandong Provincial Qianfoshan Hospital.

Inclusion and exclusion criteria

Inclusion criteria: patients who met the clinical diagnostic criteria of PTC and were confirmed to have CLNM by lymph node biopsy; patients with primary thyroid tumors; patients with detailed clinical data; patients who had not received any surgeries within 6 months before admission [13].

Exclusion criteria: patients comorbid with Hashimoto's thyroiditis; patients with clinical manifestations, such as obvious hypothyroidism or hyperthyroidism; patients comorbid with serious organic or infectious diseases; pregnant or lactating women; patients with dysfunction of important organs or blood system diseases; patients with poor-quality ultrasonic images due to the special location of nodules.

Relevant indicators and data collection

The data were collected in each patient, including age, sex, body mass index (BMI), focus diameter, vascular invasion, microcalcification, capsule infiltration, multiple foci, peak intensity (PI), time to peak (TTP), mean transit time (MTT), triiodothyronine (T3), Triiodothyronine 4 (T4), thyroid-stimulating hormone (TSH), and carcinoembryonic antigen (CEA). All ultrasound data were tested by IU 22 color Doppler diagnostic instrument (Amsterdam, The Netherlands, Philips).

Diagnostic criteria for CLNM

CT examination showed cystic changes in the lymph nodes, fine granular calcification, and enhancement of the edges. Otherwise, the maximum value of the transverse diameter of the lymph nodes was observed, and CLNM was also considered when submandibular and subchin lymph nodes measured over 10 mm, tracheal or esophageal sulcus lymph nodes measured over 5 mm, or measured over 8 mm in other areas.

Outcome measures

Primary outcome measures: Logistic regression analysis was conducted to identify the risk factors of CLNM in PTC patients. According to the independent risk factors obtained after regression, receiver operating characteristic (ROC) curves were plotted to evaluate their diagnostic efficacy.

Secondary outcome measures: The clinical data, ultrasound parameters, and levels of T3, T4, TSH, and CEA were compared between the two groups.

Statistical analyses

GraphPad Prism 8 software was used for data visualization, and SPSS20.0 software for statistical analyses. Counted data (rate) were analyzed using the chi-square test. Measured data (mean ± standard deviation) were analyzed using independent-samples t test for intergroup comparison and paired t test for intra-

Table 1. Clinical data

Factor	Transfer group (n=54)	Non-transfer group (n=125)	χ^2 value	*P* value
Age			0.191	0.661
≥45 years old	24	60		
<45 years old	30	65		
Gender			0.124	0.724
Male	15	38		
Female	39	87		
BMI			1.273	0.259
≥25 kg/m^2	22	40		
<25 kg/m^2	32	85		
Focus diameter			41.948	<0.001
≥10 mm	38	25		
<10 mm	16	100		
Microcalcification			6.468	0.011
Yes	43	75		
No	11	50		
Capsular infiltration			6.728	0.001
Yes	15	15		
No	39	110		
Multiple foci			22.448	<0.001
Yes	25	17		
No	29	108		

Note: BMI: body mass index.

group comparison. Logistic regression analysis was conducted to identify risk factors for CLNM in patients. ROC curves were plotted to analyze the efficacy of the risk factors for predicting CLNM. P<0.05 was considered a significant difference.

Results

Clinical data

According to inter-group comparison of clinical data, the transfer group had a higher proportion of large focus diameter, microcalcification, capsule infiltration, and multiple foci than the non-transfer group (P<0.05), but the two groups were not significantly different regarding other clinical data (P>0.05, **Table 1**).

Comparison of ultrasound parameters

According to comparison of ultrasound parameters between the two groups, the transfer group showed notably lower PI, TTP, and MTT than the non-transfer group (P<0.001, **Figure 1**). A detailed visualization of the Time-Signal intensity curves (TIC) obtained from ultrasound imaging is presented in **Figure 2**. **Figure 2A** presents the in-lesional images alongside their corresponding TICs, illustrating signal intensity fluctuations over time within the lesion of a patient. These curves are representative of the dynamic vascular patterns that occur during the contrast uptake and washout phases, with specific annotations detailing PI, sharpness, and area under the curve (AUC). **Figure 2B** illustrates the perilesional images and their associated TICs, delineating signal variations in the tissue surrounding the lesion. The graphs exhibit distinct peaks and troughs, reflecting the contrast behavior at the periphery of the lesion. These TICs are instrumental in quantifying the vascular characteristics of PTC and may offer insight into the presence of CLNM, with the quantitative differences between the metastasis and non-transfer groups being statistically significant.

Comparison of hormonal and tumor markers

The hormone indexes and tumor markers collected from the two groups were compared. According to the results, the two groups were not significantly different in T3, T4, TSH, or CEA (P>0.05, **Figure 3**).

Multivariate analysis of risk factors for CLNM

Significant indicators were assigned (**Table 2**). Then, the backward LR method was adopted for logistic regression analysis. According to the results, focus diameter, microcalcification, multiple foci, PI, TTP, and MTT were identified as independent risk factors for CLNM (**Table 3**, P<0.05).

Predictive efficacy of risk factors in CLNM

ROC curves were plotted for evaluating the predictive efficacy of the risk factors for CLNM. According to ROC curve-based analysis, the

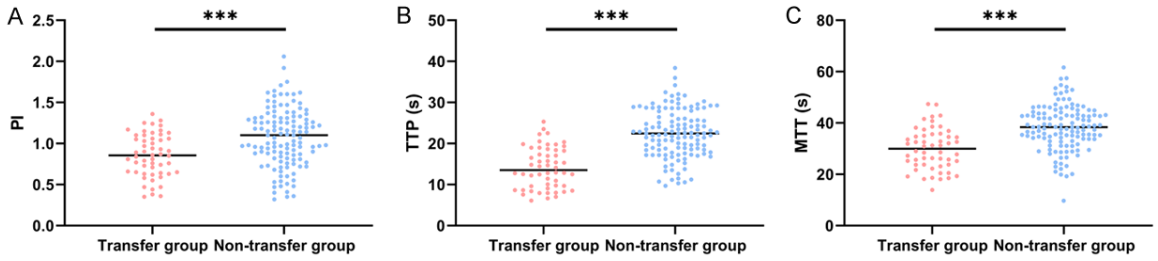

Figure 1. Comparison of PI, TTP, and MTT between the transfer group and the non-transfer group. A. Comparison of PI between the transfer group and the non-transfer group; B. Comparison of TTP between the transfer group and the non-transfer group; C. Comparison of MTT between the transfer group and the non-transfer group. PI: Peak intensity; TTP: Time to peak; MTT: Mean transit time. Compared between the two groups, ***P<0.001.

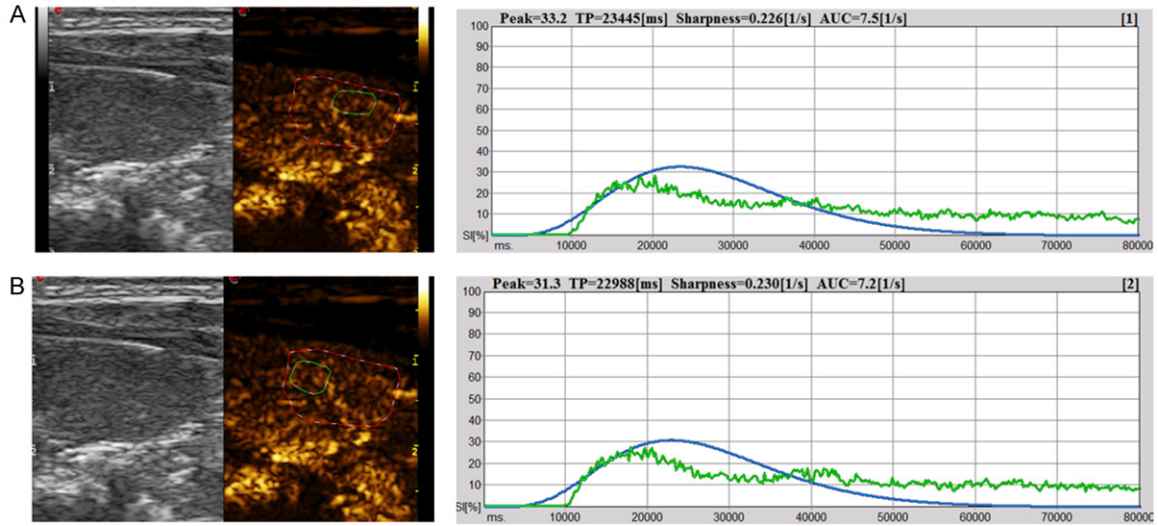

Figure 2. Intralesional and peripheral TIC curves. A. Intralesional images and TICB; B. Perilesional images and TIC. TIC: Time-Signal intensity curve; TICB: Time-Intensity Curve in the Bed.

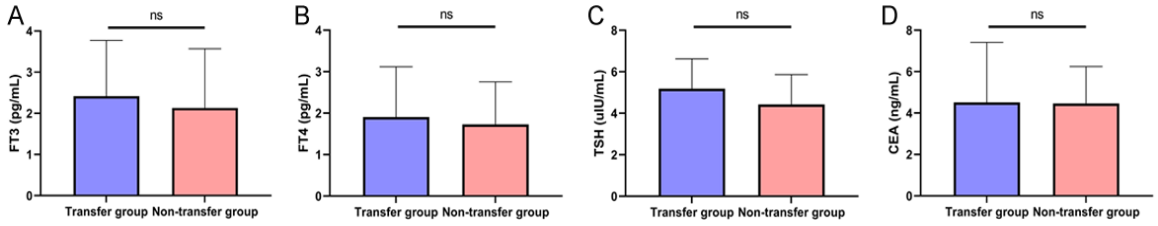

Figure 3. Comparison of hormonal and tumor markers between the transfer group and the non-transfer group. A. Comparison of free FT3 between the transfer group and the non-transfer group; B. Comparison of free FT4 between the transfer group and the non-transfer group; C. Comparison of TSH between the transfer group and the non-transfer group; D. Comparison of CEA between the transfer group and the non-transfer group. FT3: Triiodothyronine T3; FT4: Triiodothyronine T4; TSH: Thyroid-stimulating hormone; CEA: carcinoembryonic antigen. Compared between the two groups, ns indicates P>0.05.

AUCs of microcalcification, multiple foci, and PI were all smaller than 0.7; the AUCs of focus diameter and MTT were smaller than 0.8, and the AUC of TTP was 0.855, so TTP was a strong predictor for CLNM in patients with PTC (**Figure 4** and **Table 4**).

Table 2. Assignment

Factor	Assignment
Focus diameter	≥10 mm =1, <10 mm =0
Microcalcification	Yes =1, No =0
Capsular infiltration	Yes =1, No =0
Multiple foci	Yes =1, No =0
PI	<0.885=1, ≥0.885=0
TTP	<20.625=1, ≥20.625=0
MTT	<33.655=1, ≥33.655=0
Metastasis	Yes =1, No =0

Note: PI: Peak intensity; TTP: Time to peak; MTT: Mean transit time.

Discussion

Papillary thyroid carcinoma (PTC) develops slowly, without causing obvious pain during the course of development, and it has a low rate of distant metastasis and death, so many potential patients are only identified postmortem [14, 15].

The thyroid gland is an organ with abundant blood supply, and it is of great value to assess the progression of thyroid-related diseases by adopting various measures to understand the blood flow status in patients [16]. To a certain extent, PTC is prone to CLNM, which directly increases the difficulty of disease treatment and the risk of recurrence [17]. Currently, there is still a lack of effective methods for early diagnosis of PTC and early determination of CLNM. Most PTC patients already have CLNM at the time of diagnosis. Some patients have complicated ultrasonic manifestations, characterized by overlapping and intersecting features, making accurate differentiation challenging with only two-dimensional ultrasound [18]. With the development of technology, contrast-enhanced ultrasound technology has been gradually adopted for examining tumor lymph node metastasis [18]. Contrast-enhanced ultrasound can help observe and evaluate the blood perfusion in tissues through contrast agent. There is abundant blood supply in malignant tumors, and the contrast agent flowing through such blood vessels can cause abnormal related parameters, which can provide a reference for the clinical judgment of the nature of foci [19]. In this study, the PI, TTP, and MTT of PTC patients with or without CLNM were quantified. Among the quantitative parameters of contrast-enhanced ultrasound, PI represents the total number of microbubbles entering the tumor vascular bed, that is, the most significant signal intensity enhancement in the region of interest can reflect the maximum dose of contrast agent reaching this region and reflect the blood flow of local tissues to some extent [20]. TTP and MTT can help evaluate the neovascularization and cell proliferation in thyroid nodules [21, 22]. In this study, patients with metastasis exhibited lower PI, TTP, and MTT than those without, which indicated correlations of PI, TTP, and MTT with CLNM in PTC patients. This is possibly due to the lack of blood supply after CLNM in PTC. After CLNM, the demand for blood flow of the tumor is reduced. That is, the lower the blood flow signal of the focus, the lower the contrast enhancement of the focus, the shorter the TTP and MTT, and the smaller the PI. Gu et al. revealed lower PI, TTP, and MTT in malignant thyroid nodules of PTC than those in benign nodules [23]. In addition, Li et al. found that TTP and MTT in patients with choroid metastasis were significantly shorter than in those with no choroid metastasis [24]. These studies all indicate a certain value of PI, TTP, and MTT in tumor metastasis. Compared to Li's study, our study has the following novelties and advantages: First, we used a more novel ultrasound technique and a more refined measurement technique, which improved the accuracy and detailed description of the measurement [25]. Second, our sample size was larger, which allowed us to have ultrasound parameters according to representativeness. In addition, we analyzed other ultrasound parameters that were not included in Li's study, thus providing a more detailed understanding of CLNM. Our study also includes direct comparison of different ultrasound parameters and comparative analysis with other diagnostic methods, which are important contributions. Our findings have more direct or practical applications in clinical practice, such as treatment strategy planning or follow-up programs. In addition, we used more sophisticated statistical methods to analyze the data, leading to more reliable or nuanced conclusions.

The typical feature of PTC is the presence of a hard mass in the thyroid gland, and some patients already have CLNM at the time of initial diagnosis. This study aimed to analyze the risk factors associated with CLNM. The results indicated that several factors, including focus

Table 3. Multivariate logistic analysis

Factor	β	SE	Wald	*P* value	OR value	95% CI of EXP (B)	
						Lower limit	Upper limit
Focus diameter	2.828	0.630	20.128	<0.001	16.908	4.916	58.159
Microcalcification	1.208	0.593	4.145	0.042	3.345	1.046	10.699
Capsular infiltration	0.506	0.649	0.607	0.436	1.658	0.465	5.918
Multiple foci	3.300	0.750	19.335	<0.001	27.101	6.227	117.957
PI	1.806	0.647	7.795	0.005	6.088	1.713	21.635
TTP	1.892	0.649	8.490	0.004	6.631	1.858	23.670
MTT	1.468	0.532	7.621	0.006	4.339	1.531	12.302

Note: PI: Peak intensity; TTP: Time to peak; MTT: Mean transit time; OR: odd ratio; CI: confidence interval; SE: standard error.

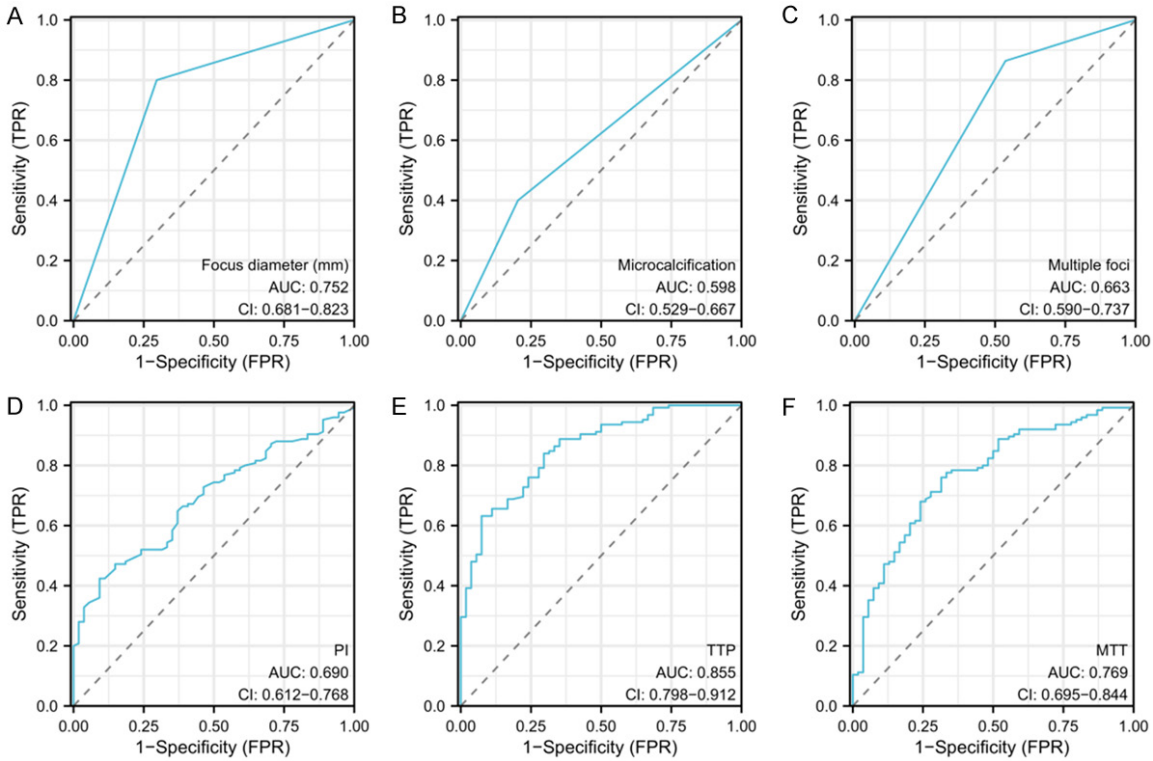

Figure 4. ROC curves of risk factors in predicting lymph node metastasis in patients. A. ROC curve of focus diameter in predicting lymph node metastasis in patients; B. ROC curve of microcalcification in predicting lymph node metastasis in patients; C. ROC curve of multiple foci in predicting lymph node metastasis in patients; D. ROC curve of PT in predicting lymph node metastasis in patients; E. ROC curve of TTP in predicting lymph node metastasis in patients; F. ROC curve of MTT in predicting lymph node metastasis in patients. ROC: Receiver operating characteristic curve; PI: Peak intensity; TTP: Time to peak; MTT: Mean transit time; FPR: false positive rate; TPR: true positive rate; AUC: area under curve; CI: confidence interval.

diameter, presence of microcalcification, multiple foci, PI, TTP, and MTT, were independent risk factors for CLNM in PTC patients. Nodules with a diameter of ≥10 mm were more susceptible to CLNM due to the presence of rich blood vessels in the tumor, which accelerates nodule growth. As nodules grow and enlarge, the likelihood of invasion of surrounding lymphatic vessels increases, thereby increasing the risk of metastasis [26-28]. Microcalcification contributes to the rapid growth of cancer cells and the proliferation of blood vessels and fibrous tissue within nodules [17]. The presence of multiple cancer foci in glands is a common indication of PTC metastasis, as confirmed by numerous studies [29, 30]. Additionally, this study discovered for the first time that PI, TTP, and MTT were independent risk factors for CLNM in PTC. This

Table 4. ROC curve parameters

Predictor variable	Area under curve (AUC)	Confidence interval (CI)	Sensitivity (%)	Specificity (%)	Youden index (%)
Focus diameter	0.752	0.681-0.823	80.00	70.37	50.37
Microcalcification	0.598	0.333-0.471	40.00	79.63	19.63
Multiple foci	0.663	0.263-0.410	8640	46.29	32.69
PI	0.690	0.612-0.768	42.40	90.74	33.14
TTP	0.855	0.798-0.912	63.20	92.59	55.79
MTT	0.769	0.695-0.844	76.00	68.51	44.51

Note: PI: Peak intensity; TTP: Time to peak; MTT: Mean transit time; ROC: receiver operating characteristic.

can be attributed to the reduced blood flow rate resulting from the presence of rich new blood vessels after CLNM, leading to a decrease in PI, TTP, and MTT. Furthermore, the study revealed a high clinical value of TTP for predicting CLNM in PTC patients, with an AUC of 0.855.

This study demonstrated the value of PI, TTP, and MTT in the prediction of CLNM in patients with PTC through a retrospective study. However, there are some limitations. First, it was a single-center study, which may limit the generalizability of the results. Second, of note, the number of eligible samples was significantly reduced after screening according to the inclusion and exclusion criteria. This may have affected the representativeness and statistical power of the findings. Due to the reduced sample size, some analyses may have failed to adequately reveal potential risk factors and their relationships. In addition, we were unable to collect patient survival data, and thus the relationship between PI, TTP, and MTT and patient survival requires further validation. Given these limitations, we hope to conduct additional experiments in the future to refine the findings and validate these preliminary findings.

To sum up, PI, TTP, and MTT all decrease in PTC patients with CLNM, and TTP had a strong predictive value for CLNM in them, with an AUC of 0.855.

Disclosure of conflict of interest

None.

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References

[1] Lin RX, Yang SL, Jia Y, Wu JC, Xu Z and Zhang H. Epigenetic regulation of papillary thyroid carcinoma by long non-coding RNAs. Semin Cancer Biol 2022; 83: 253-260.

[2] Hong S, Xie Y, Cheng Z, Li J, He W, Guo Z, Zhang Q, Peng S, He M, Yu S, Xu L, Liu R, Xu T, Zhang Y, Li Y, Wang J, Lv W, Yu J and Xiao H. Distinct molecular subtypes of papillary thyroid carcinoma and gene signature with diagnostic capability. Oncogene 2022; 41: 5121-5132.

[3] Motti ML, Tafuri D, Donini L, Masucci MT, De Falco V and Mazzeo F. The role of nutrients in prevention, treatment and post-coronavirus disease-2019 (COVID-19). Nutrients 2022; 14: 1000.

[4] Pasqual E, Sosa JA, Chen Y, Schonfeld SJ, Berrington de González A and Kitahara CM. Trends in the management of localized papillary thyroid carcinoma in the United States (2000-2018). Thyroid 2022; 32: 397-410.

[5] Orsatti A, De Leo A, Chiarucci F, Simoncini G, Cremonini N, Fornelli A, Amorosa L, Maloberti T, de Biase D and Tallini G. Multifocal fibrosing thyroiditis: an under-recognized mimicker of papillary thyroid carcinoma. Endocr Pathol 2022; 33: 335-345.

[6] Wang T, Shi J, Li L, Zhou X, Zhang H, Zhang X, Wang Y, Liu L and Sheng L. Single-cell transcriptome analysis reveals inter-tumor heterogeneity in bilateral papillary thyroid carcinoma. Front Immunol 2022; 13: 840811.

[7] Li QL, Ma T, Wang ZJ, Huang L, Liu W, Chen M, Sang T, Ren XG, Tong J, Cao CL, Dong J and Li J. The value of contrast-enhanced ultrasound for the diagnosis of metastatic cervical lymph nodes of papillary thyroid carcinoma: a systematic review and meta-analysis. J Clin Ultrasound 2022; 50: 60-69.

[8] Radzina M, Ratniece M, Putrins DS, Saule L and Cantisani V. Performance of contrast-enhanced ultrasound in thyroid nodules: review of current state and future perspectives. Cancers (Basel) 2021; 13: 5469.

[9] Fang F, Gong Y, Liao L, Ye F, Zuo Z, Qi Z, Li X and Niu C. Value of contrast-enhanced ultrasound

in partially cystic papillary thyroid carcinomas. Front Endocrinol (Lausanne) 2021; 12: 783670.
[10] Chen L, Chen L, Liang Z, Shao Y, Sun X and Liu J. Value of contrast-enhanced ultrasound in the preoperative evaluation of papillary thyroid carcinoma invasiveness. Front Oncol 2022; 11: 795302.
[11] Li W, Li Y, Long M, Li J, Ma J and Luo Y. Vascularity depicted by contrast-enhanced ultrasound predicts recurrence of papillary thyroid cancer. Eur J Radiol 2023; 159: 110667.
[12] Ye F, Gong Y, Tang K, Xu Y, Zhang R, Chen S, Li X, Zhang Q, Liao L, Zuo Z and Niu C. Contrast-enhanced ultrasound characteristics of preoperative central cervical lymph node metastasis in papillary thyroid carcinoma. Front Endocrinol (Lausanne) 2022; 13: 941905.
[13] Haddad RI, Nasr C, Bischoff L, Busaidy NL, Byrd D, Callender G, Dickson P, Duh QY, Ehya H, Goldner W, Haymart M, Hoh C, Hunt JP, Iagaru A, Kandeel F, Kopp P, Lamonica DM, McIver B, Raeburn CD, Ridge JA, Ringel MD, Scheri RP, Shah JP, Sippel R, Smallridge RC, Sturgeon C, Wang TN, Wirth LJ, Wong RJ, Johnson-Chilla A, Hoffmann KG and Gurski LA. NCCN guidelines insights: thyroid carcinoma, version 2.2018. J Natl Compr Canc Netw 2018; 16: 1429-1440.
[14] Wang W, Ding Y, Jiang W and Li X. Can cervical lymph node metastasis increase the risk of distant metastasis in papillary thyroid carcinoma? Front Endocrinol (Lausanne) 2022; 13: 917794.
[15] Baum JE, Soong L, Scognamiglio T, Margolskee EM, Hoda RS and Rao R. Cytological diagnosis of papillary thyroid carcinoma with tall cells on ThinPrep liquid-based cytology. Diagn Cytopathol 2019; 47: 541-546.
[16] Gao X, Luo W, He L, Cheng J and Yang L. Predictors and a prediction model for central cervical lymph node metastasis in papillary thyroid carcinoma (cN0). Front Endocrinol (Lausanne) 2022; 12: 789310.
[17] Mao J, Zhang Q, Zhang H, Zheng K, Wang R and Wang G. Risk factors for lymph node metastasis in papillary thyroid carcinoma: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2020; 11: 265.
[18] Luo ZY, Hong YR, Yan CX, Wang Y, Ye Q and Huang P. Utility of quantitative contrast-enhanced ultrasound for the prediction of lymph node metastasis in patients with papillary thyroid carcinoma. Clin Hemorheol Microcirc 2022; 80: 37-48.
[19] Wei Y, Niu Y, Zhao ZL, Cao XJ, Peng LL, Li Y and Yu MA. Effectiveness of lymphatic contrast enhanced ultrasound in the diagnosis of cervical lymph node metastasis from papillary thyroid carcinoma. Sci Rep 2022; 12: 578.
[20] Wang J, Yang Y, Liu X and Duan Y. Intraoperative contrast-enhanced ultrasound for cerebral glioma resection and the relationship between microvascular perfusion and microvessel density. Clin Neurol Neurosurg 2019; 186: 105512.
[21] Wildner D, Heinzerling L, Scheulen ME, Kaempgen E, Schuler G, Strobel D, Janka R, Neurath MF, Sturm J and Knieling F. Assessment of sorafenib induced changes in tumor perfusion of uveal melanoma metastases with dynamic contrast-enhanced ultrasound (DCE-US). J Cancer Res Clin Oncol 2022; 148: 955-965.
[22] Sharma A, Grover SB, Mani C and Ahluwalia C. Contrast enhanced ultrasound quantitative parameters for assessing neoadjuvant chemotherapy response in patients with locally advanced breast cancer. Br J Radiol 2021; 94: 20201160.
[23] Gu F, Han L, Yang X, Liu H, Li X, Guo K, Zhao Z, Zhou X and Luo W. Value of time-intensity curve analysis of contrast-enhanced ultrasound in the differential diagnosis of thyroid nodules. Eur J Radiol 2018; 105: 182-187.
[24] Li D, Wang Z, Chen W, Zhao Q, Li Y, Cui R, Shen L, Liu Q, Cao K, Liu Y, Wei W and Yang W. Quantitative analysis of perfusion characteristics using contrast-enhanced ultrasound in patients with choroidal metastasis. Ophthalmic Res 2022; 65: 86-93.
[25] Li X. Value of color doppler ultrasound in the evaluation of lymph node metastases in papillary thyroid carcinoma. Hainan Med J 2012; 19: 88-90.
[26] Zhao H, Huang T and Li H. Risk factors for skip metastasis and lateral lymph node metastasis of papillary thyroid cancer. Surgery 2019; 166: 55-60.
[27] Zhu F, Zhu L, Shen Y, Li F, Xie X and Wu Y. Differences in the clinical characteristics of papillary thyroid microcarcinoma located in the isthmus ≤5 mm and >5 mm in diameter. Front Oncol 2022; 12: 923266.
[28] Zhu Q, Shao Z, Zhang X and Xu D. Correlation between ultrasonic features of medullary thyroid carcinoma and cervical lymph node metastasis. Ultrasound Med Biol 2021; 47: 967-972.
[29] Liu C, Xiao C, Chen J, Li X, Feng Z, Gao Q and Liu Z. Risk factor analysis for predicting cervical lymph node metastasis in papillary thyroid carcinoma: a study of 966 patients. BMC Cancer 2019; 19: 622.
[30] Qiao L, Dong C, Zhang N and Ma BL. Analysis of lymph node jump metastasis in papillary thyroid carcinoma. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2018; 32: 522-526.