Research Article

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Clinical Value of Contrast-Enhanced Ultrasonography In Tiny Nodules Of Thyroid

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Abstract

Purpose

To analyze the accuracy of contrast-enhanced ultrasonography (CE-US) in diagnosing tiny nodules of thyroid. To explore the clinical value of CE-US in the diagnosis of tiny nodules of thyroid.

Methods

Patients undergoing CE-US and ultrasound-guided fine needle aspiration (US-FNA) of tiny nodules (≤1cm) were selected for the study; this included patients with papillary thyroid microcarcinoma (PTMC), nodular goiter (NG) and subacute thyroiditis (SAT). All patients underwent color Doppler ultrasonography (CD-US) after which thyroid image reporting and data system (TI-RADS) grading were done. The results of the CE-US were analyzed using descriptive statistics. The cytopathological results from the US-FNAs were the gold standard used to confirm the diagnoses.

Results

A total of 64 patients were selected for the study. In the PTMC group (n=28), grading was as follows: TI-RADS4a, n=7; TI-RADS4b, n=15; and TI-RADS4c, n=6. More patients showed heterogeneous hypoenhancement (n=25) than heterogeneous isoenhancement (n=3) on CE-US. In the NG group (n=25) grading was as follows: TI-RADS3, n=1; TI-RADS4a, n=18; TI-RADS4b, n=6. One patient showed heterogeneous is enhancement, two patients showed heterogeneous hypoenhancement and 22 patients showed uniform is enhancement on CE-US. In the SAT group (n=11) grading was as follows: TI-RADS3, n=1; TI-RADS4a, n=8; TI-RADS4b, n=2. Fewer patients showed heterogeneous hypoenhancement (n=1) than heterogeneous is enhancement (n=10) on CE-US. The diagnostic accuracy of CD-US + CE-US differed significantly from that of CD-US alone ($p<0.05$).

Conclusions

CE-US has a high diagnostic accuracy for tiny nodules of thyroid and can be used to identify PTMC, NG, and SAT.

Keywords: Papillary Thyroid Micro carcinoma; Nodular Goiter; Subacute Thyroiditis; Contrast-Enhanced Ultrasonography; Tiny Nodule

Introduction

Thyroid carcinoma is the most common malignant tumor of the endocrine system, showing a gradual rise in morbidity during recent years and increasingly gaining the attention of clinicians and researchers. Currently, thyroid carcinoma has outpaced all malignant tumors in terms of heightened morbidity [1]. The soaring rate of thyroid carcinoma is primarily due to papillary carcinoma, especially in its earliest stages (ie micro carcinoma) [2]. According to the latest Surveillance, Epidemiology, and End Results (SEER) data, nearly 90% of thyroid carcinomas are papillary type[3]. Thus, research aimed at thyroid papillary micro carcinoma (PTMC) is of utmost importance. Metastasis of PTMC to cervical lymph nodes reportedly ranges from 30-70% [4-6]. Some patients experience early postsurgical local recurrences or even present with distant metastases to lungs or bone [7]. The present study was undertaken to gauge the accuracy of diagnosing PTMC.

Contrast-enhanced ultrasonography (CE-US) is a non-invasive modality used in many organs (eg, liver and kidneys) to differentiate benign and malignant tumors [8-9]. For the present study, CE-US was applied to thyroid tiny nodules in order to assess its utility in the differential diagnosis of PTMC.

Materials and Methods

Patient Population

Between January 2017 and December 2018, patients undergoing CE-US and ultrasound-guided fine needle aspiration (US-FNA) of a single thyroid tiny nodules (maximum diameter≤ 1.0 cm) at the Department of Ultrasound Diagnosis were selected for the study. The patients' ages ranged from 22-65 years (mean, 35.3±2.3 years), and 48 were women. This included patients with papillary thyroid microcarcinoma (PTMC) (maximum diameter, 0.4-1.0 cm), nodular goiter (NG) (maximum diameter, 0.4-1.0 cm) and subacute thyroiditis (SAT) (maximum diameter, 0.5-1.0 cm). Each diagnosis was cytopathologically confirmed. No patient had FNA contraindications. Pregnancy and tiny nodules showing cystic degeneration were grounds for exclusion.

Equipment and Methods

Cd-Us, Ce-Us

An IU22 color Doppler ultrasonic diagnosis system (Philips Medical Systems, Amsterdam, Netherlands) with a probe frequency of 5-12 MHz was used. With patients in the supine position, the thyroid glands were scanned to determine size, number, location, border, shape, internal echo, blood flow and calcification, as well as the aspect ratio (>1) and attenuation of the thyroid tiny nodules. Then, thyroid image reporting and data system (TI-RADS) grading was as follows: TI-RADS1, negative; TI-RADS2, benign; TI-RADS3, probably benign (no suspicious US features); TI-RADS4a, one suspicious US feature; TI-RADS4b, two suspicious US features; TI-RADS4c, three or four suspicious US features; TI-RADS5, five suspicious US features [7]. Prior to US-FNA, each tiny nodule was studied via CE-US. Each of the recruited patients harbored a single suspicious thyroid tiny nodules.

CE-US was performed by injecting a 1-1.5 ml bolus of a contrast medium (SonoVue; Bracco Diagnostics, Milan, Italy) into the ulnar vein, followed by 3 minutes of continuous observation. The contrast arrival time, enhancement intensity, internal enhancement, edge enhancement, and wash-out time were recorded.

Cytopathological Examination

US-FNA was performed on each tiny nodule to confirm the diagnosis. Cytopathological evaluations of the specimens obtained by US-FNA were performed by two pathologists as a routine medical procedure in the Department of Pathology.

Benign Vs Malignant Thyroid Nodules

In gauging benign and malignant thyroid tiny nodules by CD-US, grades TI-RADS3 and 4a qualified as benign, whereas TI-RADS4b, 4c and 5 qualified as malignancy [10]. Each patient underwent a CD-US examination which was conducted jointly by two vice professors. Disagreements were resolved by discussion. The same diagnostic methods were used for each patient.

Statistical Analysis

Measurement data were expressed as mean ± standard deviation. Accuracy was calculated for each group. Between-group comparisons were achieved using a t test. All data handling relied on a standard software (SPSS v21.0; IBM, Armonk, NY, USA).

Results

Ultrasonographic Findings

A total of 64 patients were selected for the study. Using the cytopathological results of US-FNA as the gold standard, in the PTMC group (n=28), grading with CD-US was as follows: TI-RADS4a, n=7; TI-RADS4b, n=15; and TI-RADS4c, n=6. On CE-US, more patients (n=25) showed heterogeneous hypoenhancement (Figure 1): Hypoechogenic lesion of the left thyroid lobe. CE-US showed heterogeneous hypoenhancements, and cytopathology showed PTMC. than heterogeneous isoenhancement (n=3). In the GN group (n=25), grading with CD-US was as follows: TI-RADS3, n=1; TI-RADS4a, n=18; and TI-RADS4b, n=6. Of those in the NG group, one patient showed heterogeneous isoenhancement, two patients showed heterogeneous hypoenhancement and 22 patients showed uniform isoenhancement on CE-US (Figure 2): Hypoechogenic lesion of the right thyroid lobe. CE-US showed uniform isoenhancement, and cytopathology showed GN In the SAT group (n=11), grading with CD-US was as follows: TI-RADS3, n=1; TI-RADS4a, n=8; and TI-RADS4b, n=2. On CE-US, fewer patients (n=1) showed heterogeneous hypoenhancement than heterogeneous isoenhancement (n=10) (Figure 3): Hypoechogenic lesion of the left thyroid lobe. CE-US showed heterogeneous isoenhancement, and cytopathology showed SAT

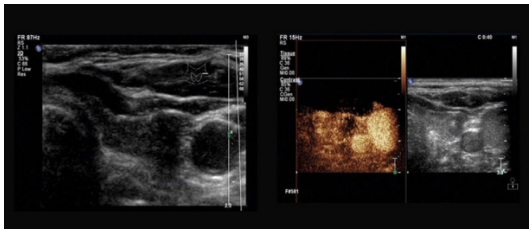

Figure 1: Hypoechogenic lesion of the left thyroid lobe. CE-US showed heterogeneous hypoenhancements, and cytopathology showed PTMC.

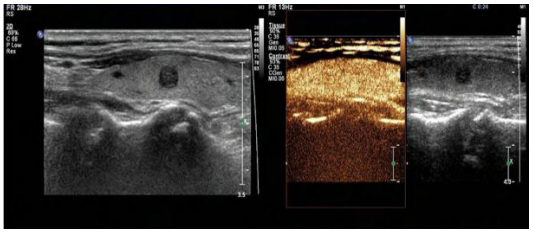

Figure 2: Hypoechogenic lesion of the right thyroid lobe. CE-US showed uniform isoenhancement, and cytopathology showed GN.

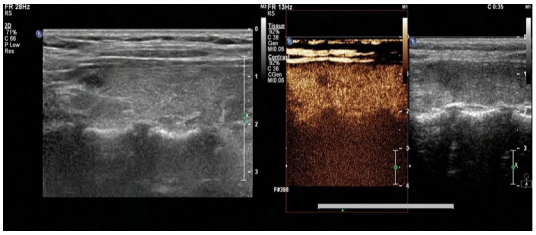

Figure 3: Hypoechogenic lesion of the left thyroid lobe. CE-US showed heterogeneous isoenhancement, and cytopathology showed SAT.

Overall Diagnostic Parameters

Diagnostic accuracies in PTMC, GN, and SAT groups were 75.00%, 76.00%, 81.82%, respectively with CD-US; and 89.29%, 88.00%, 90.91% respectively with CD-US + CE-US. In accurately diagnosing the thyroid tiny nodules, CD-US + CE-US was significantly superior to CD-US alone ($p<0.05$; Table 1).

Table 1. Diagnostic values of CD-US and CD-US + CE-US in tiny nodule of thyroid.

		(+)	(-)	Accuracy	*P*
CD-US	PTMC		7	75.00%	
CD-US + CE-US	PTMC	25	3	89.29%	P<0.05
CD-US	GN	19	6	76.00%	
CD-US + CE-US	GN	22	3	88.00%	P<0.05
CD-US	SAT	9	2	81.82%	
CD-US + CE-US	SAT	10	1	90.91%	P<0.05

*$P<0.05$, statistically different; $P>0.05$, not statistically different.

Discussion

In recent years, the frequency of PTMC has climbed rapidly, and its morbidity has dramatically increased. Although surgery for PTMC is debated, nodal metastasis of PTMC is undisputed, and the rate is high. For example, central lymph node metastasis alone ranges from 24%-64% and is associated with recurrence and death rates [11]. Such grim prospects demand high diagnostic accuracy, because surgical treatment of PTMC with metastasis is routinely recommended by thyroid specialists.

Unfortunately, the diagnostic accuracy of PTMC is low. It is often missed, or there is misdiagnosis [12-13]. At present, the chief means of diagnosis is CD-US, achieving a diagnostic accuracy of 74.2% [14]. CE-US is widely employed, but its utility in PTMC has not been carefully explored. In this study, a careful investigation of PTMC was undertaken for this purpose.

Domestic and foreign sources have reported specificities of 88-90% and sensitivities of 85-88% in assessing the thyroid using CE-US; when coupled with CD-US, the accuracy of diagnosing malignant thyroid nodules improves, perhaps reaching 96% [15-20]. Liu et al. reported that the diagnostic accuracy, specificity, sensitivity of CE-US were 81.65%, 88.00%, 88.00% respectively [21]. However, the diagnostic accuracy of CE-US is related to the size of thyroid lesions; the larger the lesion, the higher the diagnostic accuracy [22]. In our analysis, the diagnostic accuracy (88.00%-90.91%) of CD-US+CE-US in thyroid nodules was slightly lower than figures cited elsewhere. This is largely explained by the fact that our study included nodules ≤ 1 cm, whereas others included lesions >1 cm. Limiting the lesions size most likely reduced the diagnostic accuracy of CE-US. We were able to show a statistical difference between CD-US + CE-US compared to CD-US alone. Our results indicate that combined testing compensates for the lower accuracy of either method alone and increases the overall accuracy in diagnosing thyroid tiny nodules.

In our study PTMC mainly appeared with heterogeneous hypoenhancement on CE-US, which is consistent with other scholars' research [23-24]. As a result of thyroid tumor neovascularization, pathological vessels differ significantly from normal vessels. A lack of muscle and nerve support, vascular dysfunction, or tortuosity may lead to low enhancement of the contrast agent [25-26]. In our study, 3 case of PTMC was misdiagnosed as SAT due to heterogeneous isoenhancement. The main reason for this is when the blood supply of PTMC is rich it can show isoenhancement or hyper enhancement.

GN mainly showed uniform isoenhancement by CE-US because GN is a benign lesion without tumor neovascularization. Therefore, it results in a consistent contrast pattern with the surrounding glands. In our study, 3 cases of GN were misdiagnosed, and one case was misdiagnosed as SAT due to the appearance of heterogeneous is enhancements. The heterogenous is enhancements may have been caused by heterogeneous local liquefaction or necrosis of GN. Another 2 case was misdiagnosed as PTMC due to the appearance of heterogeneous hypoenhancements; thought to be due to showing old hemorrhage of GN.

SAT mainly appeared with heterogeneous isoenhancement with CE-US. This is mainly due to the heterogeneous invasion of inflammatory cells in the thyroid, the presence of normal glands in the inflamed area, and the lack of new blood vessels; thus appearing as a heterogeneous isoenhancement [27]. In our study, 1 cases of SAT were misdiagnosed as PTMC due to the heterogeneous hypoenhancement. When SAT is progressing rapidly, and the normal gland is small or absent, it sometimes appears with heterogeneous hypoenhancement. This is the main reason for misdiagnosis.

This study has the following limitations. Firstly, this retrospective study did not include tiny nodules with cystic degeneration because tiny nodules with cystic degeneration were more difficult to diagnose accurately on CE-US. Secondly, there was a small sample size. A larger sample size is needed to verify the conclusion of this study. Finally, the pathological gold standard in this study was cytopathology, not histopathology. Therefore, there may be errors in the diagnosis of specific inflammation and tumors. Histopathology will be selected in future research work.

Conclusion

CE-US is a simple and rapid non-invasive examination that can greatly improve the diagnostic accuracy of tiny nodule of thyroid. The three diseases of PTMC, GN and SAT have different imaging features by CE-US, which can be used to identify them.

Ethical Statements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study.

References

1. D Xu, X Lv, S Wang and W Dai (2014) "Risk factors for predicting central lymph node metastasis in papillary thyroid microcarcinoma," International journal of clinical and experimental pathology 7: 6199-6205.
2. A Y Chen, A Jemal and E M Ward (2009) "Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005," Cancer 115: 3801-3807.
3. L Davies and H G Welch (2006) "Increasing incidence of thyroid cancer in the United States, 1973-2002," JAMA 295: 2164-2167.
4. Y C Lim, E C Choi, Y H Yoon, E H Kim and B S Koo (2009) "Central lymph node metastases in unilateral papillary thyroid microcarcinoma," The British journal of surgery 96: 253-257.
5. Giuseppe Mercante, Andrea Frasoldati, Corrado Pedroni, Debora Formisano, Luigi Renna, et al. (2009) "Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients," Thyroid : official journal of the American Thyroid Association 19: 707-716.
6. Celestino P Lombardi, Rocco Bellantone, Carmela De Crea, Nunzia C Paladino, Guido Fadda, et al. (2010) "Papillary thyroid microcarcinoma: extrathyroidal extension, lymph node metastases, and risk factors for recurrence in a high prevalence of goiter area," World journal of surgery 34: 1214-1221.
7. M Varsavsky, B M Cortés, G Alonso, M A García and T M Muñoz (2011) "Metastatic adenopathy from a thyroid microcarcinoma: final diagnosis of a presumed paraganglioma," Endocrinología y nutrición : órgano de la Sociedad Española de Endocrinología y Nutrición 58: 143-144.
8. Giorgia Tedesco, Alessandro Sharon, Giulio Rizzo, Annamaria Grecchi, Ilaria Testa, et al. (2019) "Clinical use of contrast-enhanced ultrasound beyond the liver: a focus on renal, splenic, and pancreatic applications," Ultrasonography 38: 278-288.
9. Maria Franca Meloni, Amanda Smolock, Vito Cantisani, Mario Bezzi, Ferdinando D'Ambrosio, et al. (2015) "Contrast enhanced ultrasound in the evaluation and percutaneous treatment of hepatic and renal tumors," European journal of radiology 84: 1666-1674.
10. Jin Young Kwak, Kyung Hwa Han, Jung Hyun Yoon, Hee Jung Moon, Eun Ju Son, et al. (2011) "Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk," Radiology 260: 892-899.
11. S Y Cho, T H Lee, Y H Ku, H I Kim, G H Lee, et al. (2015) "Central lymph node metastasis in papillary thyroid microcarcinoma can be stratified according to the number, the size of metastatic foci, and the presence of desmoplasia," Surgery 157: 111-118.
12. B Li, Y Zhang, P Yin, J Zhou and T Jiang (2016) "Ultrasonic features of papillary thyroid microcarcinoma coexisting with a thyroid abnormality," Oncology letters 12: 2451-2456.
13. Yasuhiro Ito, Chisato Tomoda, Takashi Uruno, Yuuki Takamura, Akihiro Miya, et al. (2004) "Papillary microcarcinoma of the thyroid: how should it be treated," World journal of surgery 28: 1115-1121.
14. Z Zhao, Z Zhao, J Ma and S Jing (2015) "Clinical significance of ultrasonography in the diagnosis of central clearing of papillary thyroid carcinoma," Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery 29: 538-541.
15. B Sun, L Lang, X Zhu, F Jiang, Y Hong and L He (2015) "Accuracy of contrast-enhanced ultrasound in the identification of thyroid nodules: a meta-analysis," International journal of clinical and experimental medicine 8: 12882-12889.
16. D Yu, Y Han and T Chen (2014) "Contrast-enhanced ultrasound for differentiation of benign and malignant thyroid lesions: meta-analysis," Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 151: 909-915.
17. R N Zhao, B Zhang, X Yang, Y X Jiang, X J Lai and X Y Zhang (2015) "Logistic Regression Analysis of Contrast-Enhanced Ultrasound and Conventional Ultrasound Characteristics of Sub-centimeter Thyroid Nodules," Ultrasound in medicine & biology 41: 3102-3108.
18. F Li and H Luo (2013) "Comparative study of thyroid puncture biopsy guided by contrast-enhanced ultrasonography and conventional ultrasound," Experimental and therapeutic medicine 5: 1381-1384.
19. Yu-Zhi Zhang, Ting Xu, Hai-Yan Gong, Cui-Ying Li, Xin-Hua Ye, et al. (2016) "Application of high-resolution ultrasound, real-time elastography, and contrast-enhanced ultrasound in differentiating solid thyroid nodules," Medicine 95: e5329.
20. Y Zhang, P Zhou, S M Tian, Y F Zhao, J L Li, et al. (2017) "Usefulness of combined use of contrast-enhanced ultrasound and TI-RADS classification for the differentiation of benign from malignant lesions of thyroid nodules," European radiology 27: 1527-1536.
21. Q Liu, J Cheng, J Li, X Gao and H Li (2018) "The diagnostic accuracy of contrast-enhanced ultrasound for the differentiation of benign and malignant thyroid nodules: A PRISMA compliant meta-analysis," Medicine 97: e13325.
22. Huaqun Zhao, Xueling Liu, Bei Lei, Ping Cheng, Jian Li, et al. (2019) "Impact of thyroid nodule sizes on the diagnostic performance of Korean thyroid imaging reporting and data system and contrast-enhanced ultrasound," Clinical hemorheology and microcirculation 72: 317-326.
23. J Zhan and H Ding (2018) "Application of contrast-enhanced ultrasound for evaluation of thyroid nodules," Ultrasonography 37: 288-297.

24. Hong Yan Chen, Wei Yan Liu, Hui Zhu, Dao Wen Jiang, Dong Hua Wang, et al. (2016) "Diagnostic value of contrast-enhanced ultrasound in papillary thyroid microcarcinoma," Experimental and therapeutic medicine 11: 1555-1562.
25. X Y Meng, Q Zhang, Q Li, S Lin and J Li (2014) "Immunohistochemical levels of cyclo-oxygenase-2, matrix metalloproteinase-9 and vascular endothelial growth factor in papillary thyroid carcinoma and their clinicopathological correlations," The Journal of international medical research 42: 619-627.
26. X F Sun and H Zhang (20016) "Clinicopathological significance of stromal variables: angiogenesis, lymphangiogenesis, inflammatory infiltration, MMP and PINCH in colorectal carcinomas," Molecular cancer 5: 43.
27. Marek Ruchala, Ewelina Szczepanek-Parulska, Ariadna Zybek, Jerzy Moczko, Agata Czarnywojtek, et al. (2012) "The role of sonoelastography in acute, subacute and chronic thyroiditis: a novel application of the method," European journal of endocrinology 166: 425-432.