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Research article

Value of time-intensity curve analysis of contrast-enhanced ultrasound in the differential diagnosis of thyroid nodules

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ABSTRACT

Objective: To assess the feasibility of time-intensity curve (TIC) analysis of contrast-enhanced ultrasound (CEUS) in demonstrating features of benign and malignant thyroid nodules.

Methods: CEUS images of 98 patients with 103 thyroid nodules were retrospectively analyzed. The final diagnosis was confirmed by histology after surgical excision, or cytology after fine needle aspiration (FNA). Among the benign nodules, which were confirmed using cytology and not surgically removed, those with a > 50% cystic component that showed no changes for 1 year on follow-up US, were diagnosed as clinically benign nodules. Similarly, nodules with a < 50% cystic component that were aspirated twice and showed no changes for 1 year on follow-up US were also regarded as clinically benign nodules. TIC parameters, including perfusion parameters of relative values (RV) of peak intensity (PI) (△PI), RV of rise time (△RT), RV of time to peak (△TTP), RV of maximum slope coefficient (MSC) of wash-in (△MSC_{WI}), RV of area under the rising curve (△AUC_R), clearance parameters of RV of area under the falling curve (△AUC_F), RV of MSC of washout (△MSC_{WO}), comprehensive parameters of RV of mean transit time (△MTT), and area under the falling curve (△AUC_F) were observed.

Results: Compared with benign thyroid nodules, malignant nodules on TIC analysis of CEUS showed a lower △PI (119.73 (115.34, 129.7), −15.82 (−17.7, -4.31)), later △RT (−0.27 (−0.51, −0.2), 0.58 (−0.26, 0.65)) and △TTP (−0.52 (−0.55, −0.36), 0.69 (−0.04, 0.74)), gentler △MSC_{WI} (6.18 (5.29, 7.44), −6.1 (−7.6, 2.14)), and smaller △AUC_R (75.7 (56.95, 93.22), −88.43 (−108.89, −73.21)) in perfusion parameters; a smaller △AUC_F (112.92 (87.77, 137.58), −75.55 (−105.28, −59.32)) in clearance parameters; and a smaller △AUC (181.7 (151.50, 219.06), −160.64 (−200.08, −144.11)), and an earlier △MTT (2.00 (1.85, 3.14), −2.09 (−2.48, −0.95)) in comprehensive parameters ($P < 0.05$). Multivariate analysis of RV of TIC parameters demonstrated that △MSC_{WI} (OR = 0.112; 95% confidence interval [CI], 0.025–0.507) and △MTT (OR = 0.099; 95% CI, 0.028–0.346) were protective factors.

Conclusions: TIC of CEUS is a very promising and valuable technique for differentiating benign and malignant thyroid nodules.

1. Introduction

Nodular disease of the thyroid gland is a prevalent disease observed in 68% of the healthy population on high frequency ultrasound (US) [1]. The clinical importance of thyroid nodules lies in the need to exclude thyroid cancer, which currently occurs in 10%–15% of clinically identified nodules [2–4] and has been increasing in incidence in all ethnicities [5–7]. The health care costs of thyroid cancer will continue to escalate with the increasing incidence.

There are a number of therapeutic options for thyroid nodules,

Abbreviations: TIC, time-intensity curve; CEUS, contrast-enhanced ultrasound; US, ultrasound; FNA, fine needle aspiration; RV, relative values; PI, peak intensity; RT, rise time; TTP, time to peak; MSC_{WI}, the maximum slope coefficient of wash-in; MSC_{WO}, the maximum slope coefficient of washout; AUC, area under the curve; AUC_R, area under the rising curve; AUC_F, area under the falling curve; MTT, mean transit time; △PI, relative values of peak intensity; △RT, relative values of rise time; △TTP, relative values of time to peak; △MSC_{WI}, relative values of the maximum slope coefficient of wash-in; △MSC_{WO}, relative values of the maximum slope coefficient of washout; △AUC, relative values of area under the curve; △AUC_R, relative values of area under the rising curve; △AUC_F, relative values of area under the falling curve; △MTT, relative values of mean transit time

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including follow-up, thyroidectomy, radioactive iodine treatment, thyroid hormone therapy, and targeted therapy. The choice of treatment modality is based on the evaluation of the thyroid nodules. The mainstay of treatment for benign nodules is long-term follow-up. Thyroidectomy is an important part of treatment for malignant nodules. Early diagnosis and appropriate treatment can improve prognosis and reduce mortality [8,9]. Therefore, it is crucial that the malignant potential of thyroid nodules be accurately identified and differentiated.

Conventional thyroid US has been widely used to stratify the malignant risk of thyroid nodules [10]. Microcalcifications, irregular margins, and tall shape are the features with high specificities for thyroid cancer, but none of them are independently and fully predictive of malignancy [10,11].

The clinical value of contrast-enhanced ultrasound (CEUS) in showing differences between benign and malignant nodules in many organs has been demonstrated [12]. However, for thyroid nodules, the use of CEUS is still controversial. Cantisani et al. [13] reported that a heterogeneous peri-intralesional pattern followed by fast washout or absent wash-in were signs of malignant thyroid nodules. Nemec et al. [7] reported that the enhancement of malignant nodules was significantly higher than that of benign nodules. However, Giusti et al. [14] considered that CEUS had limited utility to differentiate benign and malignant thyroid nodules. The results of these studies were inconsistent and they found no unified criteria to evaluate thyroid nodules accurately.

To further extend these previous reports, the aim of this study was to evaluate the value of the time-intensity curve (TIC) of CEUS in demonstrating the features of benign and malignant thyroid nodules.

2. Materials and methods

2.1. Patient population

We retrospectively reviewed our database of patients with a diagnosis of thyroid nodules from July 2014 to August 2015. Inclusion criteria were: patients with nodules who underwent CEUS based on conventional US for whom the final diagnosis was confirmed by histology after surgical excision, or cytology after fine needle aspiration (FNA). Among the benign nodules, which were confirmed using cytology and not surgically removed, those with a > 50% cystic component that showed no changes for 1 year on follow-up US, were diagnosed as clinically benign nodules. Similarly, nodules with a < 50% cystic component that were aspirated twice and showed no changes for 1 year on follow-up US were also regarded as clinically benign nodules.

Exclusion criteria were: the amplitude of the respiratory motion was too sharp to compensate, the solid part of the nodule was not large enough to be analyzed, or the size of the nodules was such that the plane of CEUS could not show the entire nodule and its surrounding thyroid gland at the same time.

A total of 103 nodules in 98 consecutive patients (65 women and 33 men; age range: 20–69 years, mean: 43.89 years; 26 patients with benign nodules, 72 patients with malignant nodules, and no patients with both malignant and benign nodules) were included. The mean size of the nodules was 0.95 cm (range 0.3–2.9 cm). Surgery was performed on 69 nodules, and 34 nodules underwent US-guided FNA for the final diagnosis.

This retrospective study was approved by the ethics committee of our Hospital and written informed consent was obtained from all patients before undergoing CEUS.

2.2. US technique

The Mylab90 ultrasound imaging system (ESAOTE, Italy) equipped with L523 (4–13 MHZ) and L522 (5–13 MHz) linear-array probes, which allow working in fundamental B-mode and CEUS mode, respectively, were used for the examinations. All US scanning was performed by the same radiologist with over 10 years of experience in thyroid US.

As a first step, thyroid nodules were examined using gray-scale US. Patients were positioned supine with necks hyperextended to expose the anterior cervical region, and gray-scale US was performed using the L523 probe to identify each thyroid nodule and evaluate its size. Then, CEUS with a low mechanical index (MI 0.06) was performed using a L522 probe. The focus was always placed deeper than the nodules being examined to avoid microbubble disruption. The standard plane of CEUS was the section that showed both the entire nodule and as much of its surrounding thyroid gland as possible. About 1.0 ml of sulfur hexafluoride microbubbles (SonoVue, Bracco, Italy) was injected as a bolus manually at a flow of approximately 1 ml/s, followed by a 10-ml saline solution flush, via a 20-gauge intravenous cannula placed in an antecubital vein. Each real-time dynamic image lasted about 90 s after the injection of the contrast agent and was digitally stored on the machine's hard disk. During the process, all patients were asked to keep breathing lightly and slowly and to avoid swallowing.

2.3. Image analysis

The dynamic contrast-enhanced images were saved in a random order in DICOM format from the machine's hard disk and input into TomTec software (TomTec GmbH, Munich, Germany), which can draw time-intensity curves (TIC) for quantitative analysis. To avoid individual errors, two radiologists with 7 years of experience in thyroid US and CEUS, blinded to clinical and other imaging and pathology findings, analyzed the dynamic images independently. All parameters were measured three times by each reviewer and the average value was calculated.

The two radiologists were trained for 3 months to select regions of interest (ROI) freehand before assuming their roles as observers for this experiment. Two freehand designed ROI were drawn separately in the solid part of the nodule and the peripheral thyroid parenchyma, avoiding any large thyroid vessels, macro calcifications, and necrotic areas. If necessary, motion correction (which compensates for respiratory motion) was applied, which can reflect the results more accurately.

TICs were assayed using the following indices (Fig. 1):

Perfusion parameters: (1) peak intensity (PI), defined as the maximal signal intensity measured in the selected ROI (the PI of peripheral thyroid parenchyma was defined as 100%); (2) rise time (RT, in seconds), defined as the time that the curve increases from the starting point to 50% of the peak; (3) time to peak (TTP, in seconds), defined as the time from the starting point to the PI of the curve; (4) maximum

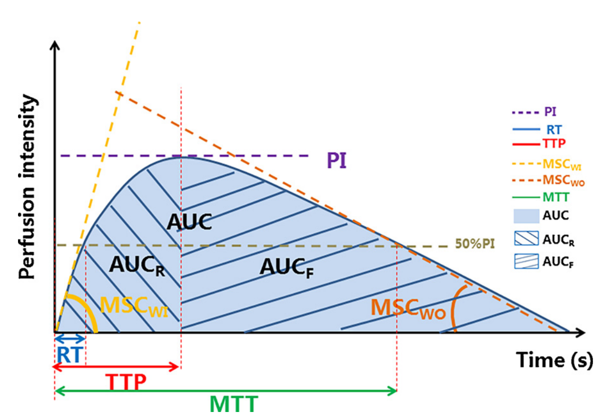

Fig. 1. Diagram of parameters on a time-intensity curve.
PI: peak intensity; RT: rise time; TTP: time to peak; MSC_{WI}: maximum slope coefficient of wash in curve; MSC_{WO}: maximum slope coefficient of washout curve; MTT: mean transit time; AUC: area under curve; AUC_R: area under the rising curve; AUC_F: area under the falling curve.