RESEARCH ARTICLE

Quantitative Analysis of Thyroid Blood Flow and Static Imaging in the Differential Diagnosis of Thyroid Nodules

Li-Ping Song*, Wen-Hong Zhang, Yang Xiang, Na Zhao

Abstract

Objective:To evaluate the performance of combined quantitative analysis of thyroid blood flow and static imaging data in the differential diagnosis of thyroid nodules. Method: Thyroid blood flow and static imaging were performed in 165 patients with thyroid nodules. Patients were divided into a benign thyroid nodule group (BTN, n=135) and a malignant thyroid nodule group (MTN, n=30) based on the results of post-surgical pathologic examination. Carotid artery thyroid transit times (CTTT), perfusion ratio of thyroid nodule blood/thyroid blood (TNB/TB), and perfusion ratio of thyroid nodule blood/carotid artery blood (TNB/CAB) were measured using thyroid blood flow imaging. The ratios between thyroid nodule and ipsilateral submandibular gland (TN/SG) and thyroid nodule and normal thyroid tissue (TN/T) were measured from thyroid static imaging. The differences between the BTN and MTN groups were compared. Results: 1) CTTT was markedly lower in the MTN group than the BTN group, the difference being statistically significant. 2) TNB/TB and TNB/CAB were both significantly higher in MTN than BTN groups. 3) TN/T was significantly lower in MTN group than BTN group. 4) TN/SG was lower in MTN group than BTN group, but the difference was not statistically significant. 5) Using the combination of CTTT and TN/T, the sensitivity, specificity and accuracy were 93.1%, 95.3% and 94.9% respectively for the diagnosis of MTN. Using the combination of CTTT, TNB/TB and TN/T, the sensitivity, specificity and accuracy changed to 89.7%, 100%, and 98.1% respectively. 6) Correlation analysis demonstrated a significant correlation between TN/T and TNB/TB (r=-0.384, *P*=0.036) and TNB/CAB (r=-0.466, *P*=0.009) in the MTN group. Conclusion: The combination of quantitative markers from thyroid blood flow and thyroid static imaging had high specificity and accuracy in differential diagnosis of benign and malignant thyroid nodules, thus providing an important imaging diagnostic approach.

Keywords: Thyroid nodules - differential diagnosis - thyroid imaging - quantitative analysis

Introduction

Thyroid nodule (TN) is a common type of thyroid lesion (Mohammadi et al., 2009) that affects all ages. It was reported about 5% of women and 1% of men in the general population had palpable thyroid nodules and the malignancy rate of these thyroid nodules could be up to 5% to 15% (Hegedus, 2004; Dean et al., 2008). Clinically differential diagnosis between benign and malignant thyroid nodules plays an important role in guiding the treatment and determining patients' prognosis.

Primary imaging approaches for differential diagnosis of benign and malignant thyroid nodules include ultrasound and radionuclide thyroid imaging (RNTI). Ultrasound exam can observe thyroid morphology, size and number of nodules, boundary sharpness, edge halo, blood supply, uniform internal echo, calcification and surrounding tissue infiltration, swollen lymph nodes, etc. Due to the apparent advantages of high resolution,

simplicity and efficiency, ultrasound exam is the preferred method for thyroid nodules diagnosis. However, due to the overlapping two-dimensional images and dependence on subjective judgement of the examiner, standard criteria have yet to be developed for the diagnosis of benign and malignant nodules (Rosario et al., 2005; Tae et al., 2007).

Since the late 20th century RNTI has been used for the differential diagnosis of benign and malignant thyroid nodules. The classification of radioactive hot, warm, cool, and cold nodules in static imaging was developed to distinguish the malignant nodule. However, the specificity of such exam is low, therefore the use of radioisotope imaging has significantly declined (Marc, 2008). To further improve the accuracy, some researchers tried to combine the imaging of thyroid pro-tumor and thyroid gland to differentiate the benign and malignant thyroid nodules (Sathekge et al., 2001), which were unfortunately shown to be ineffective and only had very limited clinical value. The aim of this study is to use the

*Department of Nuclear Medicine, the First Affiliated Hospital of Liaoning Medical College, Jinzhou, China *For correspondence: lipingsong188@163.com*

combined quantitative analysis of both thyroid blood flow imaging and static imaging data to differentiate benign and malignant thyroid nodules, which may provide valuable information for the determination of treatment plan, surgical approach and prognosis.

Materials and Methods

Study Population

We conducted a retrospective analysis of 165 consecutive patients seen at department of Nuclear Medicine, the First Affiliated Hospital of Liaoning Medical College from April 2010 to March 2011 who had thyroid nodules, underwent thyroid blood flow imaging and were confirmed by post-surgical pathology or needle biopsy. The range of age was 19 to 74 years, average 50.1 ± 15.1 years, 41 were males and 124 were females. The need of thyroid blood flow imaging was decided by the treating physician. The inclusion criteria were: (1) complaints of thyroid nodules accompanied by goiter; (2) clinically palpable thyroid nodules; (3) maximum diameter of thyroid nodule ≥ 1.0 cm under ultrasound. Exclusion criteria were: (1) incomplete clinical data; (2) maximum diameter of thyroid nodule <1.0 cm under ultrasound. All patients signed an informed consent, and the study was approved by the hospital ethical committee.

Study Subgroup

According to the post-surgical pathologic results, the patients were divided into two groups: benign thyroid nodule (BTN) group, including 35 male and 100 female patients, and malignant thyroid nodule (MTN) group, including 6 male and 24 female patients.

Imaging Instrument and Agent

The imaging instrument was dual-head coincidence circuit Infinia II SPECT/PET-CT multifunctional molecular imaging system (GE, USA). The imaging agent was $^{99m}TcO_4^-$ (Atomic Hi-Tech Co., Ltd., Beijing.)

Thyroid blood flow imaging

We used low energy high resolution parallel hole collimator with the following parameters: energy peak 140keV, window width 20%, 64×64 matrix, and magnification 2.0. Patient took supine position on the examining table with shoulder support, neck extended to expose the thyroid gland and ensure thyroid gland was located in the visual field of the detector head. $^{99m}TcO_4^-$ 370~555MBq (10-15mCi) were injected (bolus) into the contralateral cubital vein (any side if patient had bilateral nodules). At the same time the computer started dynamic acquisition of total 60 images for each patient with the speed of 2s/image.

Thyroid Static Imaging

Twenty to thirty minutes after the completion of dynamic imaging, patients underwent static imaging with following parameters: peak energy 140 keV, window width 20%, matrix 128×128 , magnification 2.0. Preset count was 3×10^5. Anteposition images were acquired using conventional approach, oblique or lateral images were also acquired if necessary. For the ratio measurement, the visual field also covered other parts of thyroid gland and salivary glands.

Quantitative Analysis of Thyroid Dynamic Imaging

Carotid artery thyroid transit time (CTTT): After the intravenous bolus injection of tracer, CTTT was defined as the time from visualization of carotid artery to the visualization of thyroid gland. Normal reference is 2.5-7.5 s.

Perfusion ratio of thyroid nodule blood/thyroid blood (TNB/TB): After the visualization of bilateral carotid artery, images were acquired to display the thyroid gland perfusion process. Using region of interest (ROI) technology, we sketched nodal site and interested area of normal thyroid tissue on the images. Average radioactivity counts from the thyroid nodule and selected thyroid tissue were calculated, and the ratio is TNB/TB.

Perfusion ratio of thyroid nodule blood/carotid artery blood (TNB/CAB): Using ROI technology, we sketched the regions of interest on both thyroid nodule and carotid artery. Average radioactivity counts in ROIs were then calculated respectively, and the ratio is TNB/CAB.

Quantitative Analysis of Thyroid Static Imaging

The uptake ratio of $^{99m}TcO_4^-$ (TN/T): The ratio between thyroid nodule and normal thyroid tissue: Using ROI technology, we sketched the regions of interest on both thyroid nodule and normal thyroid tissue. Radioactive counts in both ROIs were then calculated, and their ratio is the ratio of $^{99m}TcO_4^-$ uptake ratio.

The uptake index of $^{99m}TcO_4^-$ (TN/SG): The ratio between thyroid nodule and salivary gland: Using ROI technology, we sketched the regions of interest on both thyroid nodule and ipsilateral submandibular gland. Radioactive counts in ROIs were then calculated respectively, and the ratio is $^{99m}TcO_4^-$ uptake index.

Determine the Functional Status of TN

The distribution of imaging agents on the static images of thyroid can reflect the functional status of the nodules. According to the ability of uptaking $^{99m}TcO_4^-$, thyroid nodules were classified into hot nodule, warm nodule, cool nodule, and cold nodule.

The calculation method of sensitivity, specificity and Accuracy

sensitivity = true positive/(true positives + false negatives).

specificity = true negative/(true negatives + false positives).

Accuracy = (true positive + true negative)/(true positives + true negatives + false positives + false negatives).

Statistical Analysis

Statistical analysis was performed using SPSS (V17.0). Continuous data were summarized as mean ± standard deviation (SD). The means of two independent samples were compared using independent t test. The validity of diagnostic exam was evaluated using ROC

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Table 1. Comparison of Quantitative Markers between BTN and MTN (n=210)

Imaging Mark	BTN Group (n=180)	MTN Group (n=30)	t	*P* value
CTTT (s)	6.671±1.381	2.621±0.942	15.008	0.000
TNB/TB	0.473±0.160	2.040±0.893	18.766	0.000
TNB/CAB	0.069±0.061	0.155±0.058	6.574	0.000
TN/SG	1.051±0.350	1.048±0.454	0.084	0.811
TN/T	0.972±0.330	0.488±0.242	7.464	0.000

Table 2. Selected Threshold for each Mark and AUC

	Selected Threshold	Area under the Curve (AUC)	Standard Error
CTTT	2.621±1.413	64.40%	1.90%
TNB/TB	2.041±1.339	81.50%	1.30%
TNB/CAB	0.155±0.058	79.70%	1.30%
TN/T	0.488±0.363	72.40%	1.50%

curve. Correlation was assessed using the Pearson product-moment correlation coefficient. *P* <0.05 indicates statistical difference, *P* <0.01 indicates statistically significant difference.

Results

Patients Characteristics

Of 165 TN patients, 135 were BTN, and 30 were MTN. The BTN group consisted of 56 cases of nodular goiter (NG), 35 cases of nodular goiter cystic degeneration (NGCC), 8 cases of inflammatory nodules (IN) and 36 cases of thyroid adenoma (TA). The MTN group included 24 cases of papillary thyroid carcinoma (PTC), 5 cases of medullary thyroid carcinoma (MTC) and 1 case of undifferentiated thyroid carcinoma (UTC). The majority of patients were female at the age between 51 and 60 years.

*Characteristics and Distribution of the Thyroid Nodules*

Of the 165 TN patients, post-surgical pathology exam confirmed solitary nodules in 45 cases, including 30 cases of MTN and 15 cases of BTN. There were 120 case with multiple nodules, all of them were BTN. A total of 210 nodules were detected from the 165 patients using thyroid blood flow imaging. The malignant nodules were only shown as cold nodules, while benign nodules could be shown as any type: hot, warm, cool or cold nodules.

Comparison of Quantitative Markers between BTN and MTN Groups

Although CTTT were within the normal range for both BTN and MTN groups, the average was significant shorter in MTN group than BTN group (*P* <0.01). Also, compared to BTN group, the average TNB/TB and TNB/CAB were significantly higher (*P*<0.01), and the average TN/T was significantly lower (*P* <0.01) in MTN group. Although MTN Group also had lower TN/SG, the difference was not statistically significant (*P*> 0.05) (Table 1).
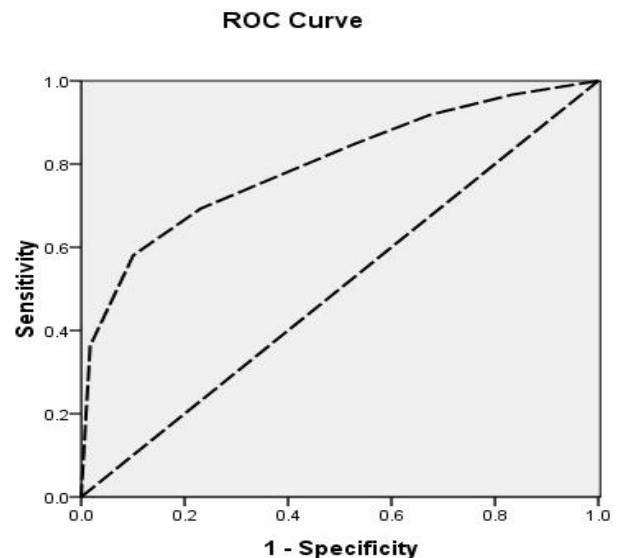
Thresholds Selection using ROC curve

There were significant differences between BTN and MTN groups on CTTT, TNB/TB, TNB/CAB and TN/T. Using the measurements of these markers from MTN
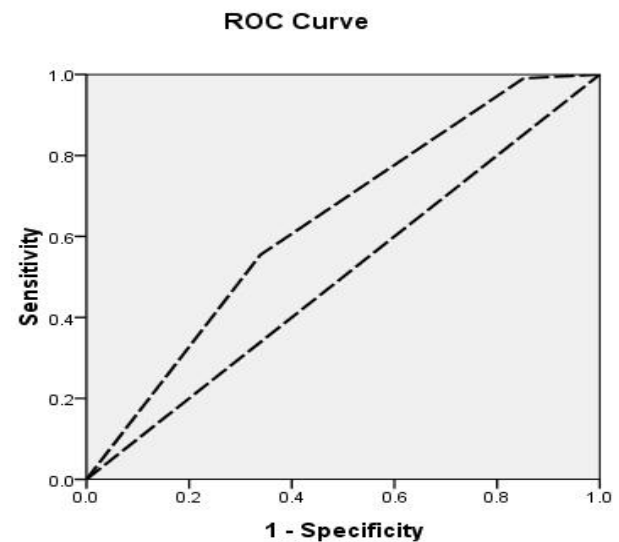
Figure 1. ROC Curve for CTTT. Note: Area Under the Curve (AUC)=64.4%, SE=1.9%. Best threshold: Mean±1.5 times the standard deviation. CTTT: Carotid artery thyroid transit time
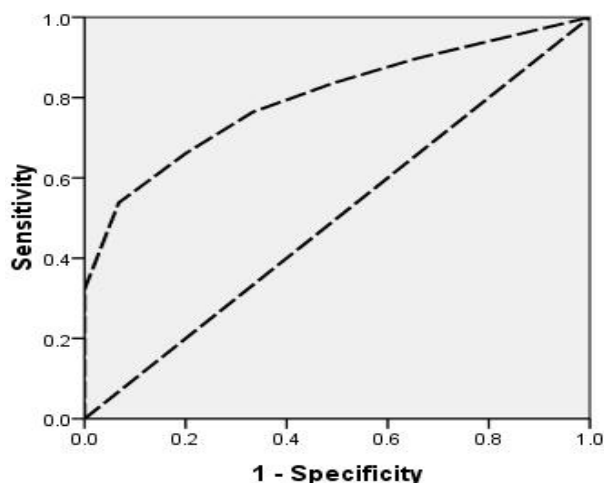

Figure 2. ROC Curve for TNB/TB. Note: AUC=81.5%, SE=1.3%. Best threshold: Mean±1.5 times the standard deviation. TNB/TB: thyroid nodule blood/thyroid blood; AUC: area under the curve

group (±s) as reference, we defined 8 thresholds ($\overline{\chi}\pm0.25$s, $\overline{\chi}\pm0.5$s, $\overline{\chi}\pm0.75$s, $\overline{\chi}\pm$s, $\overline{\chi}\pm1.25$s, $\overline{\chi}\pm1.5$s, $\overline{\chi}\pm1.75$s, $\overline{\chi}\pm2$s) for each marker and selected the best one using ROC method to diagnose the malignancy of TN (Table 2, Figure 1 to 4).

Sensitivity and Specificity using the Selected Thresholds

Using the selected thresholds, we combined the thyroid dynamic imaging quantitative markers (CTTT, TNB/TB, TNB/CAB) and static imaging marker (TN/T) to diagnose the malignancy of TN, and compared the results with the pathological diagnosis to calculate the sensitivity, specificity, and accuracy. The results are shown in Table 3.
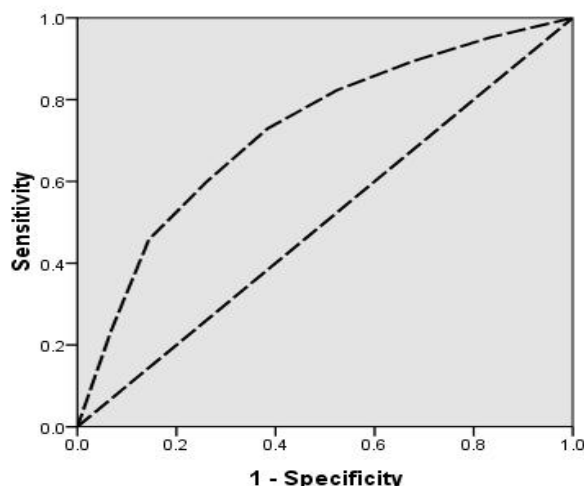
Figure 3. ROC Curve for TNB/CAB. Note: AUC=79.7%, SE=1.3%. Best threshold: Mean±1.5 times the standard deviation. TNB: thyroid nodule blood; CAB: carotid artery blood

Table 3. Sensitivity and Specificity of MTN Diagnosis using the Combination of Thyroid Dynamic and Static Imaging Markers

Combination of Markers	Sensitivity (%)	Specificity (%)	Accuracy (%)
Combination of CTTT, TNB/TB, TNB/CAB, TN/T	65.52	100	93.63
Combination of CTTT, TN/T	93.10	95.31	94.90
Combination of TNB/CAB, TN/T	72.41	95.31	91.08
Combination of TNB/TB, TN/T	89.66	96.09	94.90
Combination of CTTT, TNB/TB, TN/T	89.66	100.00	98.09
Combination of CTTT, TNB/CAB, TN/T	72.41	98.44	93.63
Combination of TNB/TB, TNB/CAB, TN/T	65.52	98.44	92.36

The correlation between the CTTT,TNB/TB,TNB/CAB and TN/T in group of MTN and BTN

Correlation analysis demonstrated a significant correlation between TN/T and TNB/TB (r=-0.384, *P*=0.036) and TNB/CAB (r=-0.466, *P*=0.009) in group of MTN. There was no apparent correlation between TN/T and CTTT (r=0.284, *P*=0.136) in group of MTN.

Correlation analysis demonstrated that there were no apparent correlation between TN/T and CTTT (r=0.066, *P*=0.463), TNB/TB (r=0.033, *P*=0.711) and TNB/CAB (r=-0.183, *P*=0.059) in group of BTN.

Discussion

Thyroid nodule is a common type of thyroid lesion, also a frequent surgical disease (Erdem et al., 2010; Alper et al., 2012). How to identify the nature of thyroid nodule prior to surgery is an urgent but yet to be resolved issue. Currently, ultrasound, thyroid scintigraphy, fine needle aspiration (FNA) biopsy are the more common methods for the diagnosis of thyroid nodules (Alper et al., 2012), and play important roles in the differentiation of benign and malignant thyroid nodules.

In this study we conducted a combined quantitative analysis of the markers from thyroid blood flow imaging and static imaging to differentiate the benign and malignant thyroid nodules. All patients enrolled had thyroid nodules

Figure 4. ROC Curve for TN/T. Note: AUC=72.4%, SE=1.5%. Best threshold: Mean±1.5 times the standard deviation. TN/T: thyroid nodule/normal thyroid tissue

with diameter ≥ 1cm. We chose CTTT, TNB/TB, and TNB/CAB as quantitative makers to reflect the blood perfusion from thyroid blood flow imaging, and TN/T from static imaging. As shown in our results, MTN had significant shorter CTTT, higher TNB/TB and TNB/CAB than BTN. This suggests most malignant thyroid nodules are rich in blood vessels, and have elevated perfusion. In the static imaging, TN/T in MTN was significantly lower than BTN, indicating the reduced ability to uptake radionuclide in MTN. As summarized in Table 3, the combination of TN/T with CTTT or TNB/TB, and the combination of CTTT, TNB / TB and TN/T had all relatively high sensitivity, specificity, and accuracy in differentiating MTN and BTN.

There have been many reports on the application of radionuclide in thyroid imaging. Cooper et al. (2009) commented that radionuclide thyroid scan has only limited value in the diagnosis of MTN, but is very valuable in ruling out MTN. If the radioactive scanning identified a high-functioning nodule, the positive predictive value for a benign lesion is quite high. Lumachi et al. (2004) reported the results of using thyroid scanning in the diagnosis of solitary thyroid nodules. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for the diagnosis of thyroid cancer were 95.8%, 21.1%, 22.6%, 95.5% and 35.7% respectively. For solitary nodule, thyroid scan alone has very low specificity.

Since first reported in 1987, ^{99m}Tc-MIBI imaging has been increasingly used in the diagnosis of thyroid cancer due to its low radiation exposure and convenience of use (Sathekge et al., 2001). However, the reported performances of ^{99m}Tc-MIBI imaging in the diagnosis of thyroid cancer were conflicting. Gudrun et al. (2012) used the combination of ^{99m}Tc-MIBI imaging and fine needle aspiration cytology to evaluate the malignancy of thyroid nodules. It was shown that for ^{99m}Tc-MIBI imaging along, the specificity and positive predictive value for the diagnosis of thyroid cancer were only 35.5% and 17.4 %, while the sensitivity and negative predictive

value were 88.2% and 95.1% respectively. This suggested if ^{99m}Tc-MIBI thyroid scan was negative, the probability of malignancy would be very small and patients might not need surgical treatment. However, Koray D et al. studied 43 patients with isolated cold thyroid nodules with diameter greater than 1.5 cm using ^{99m}Tc-MIBI thyroid scan. The sensitivity, specificity, and accuracy were 67% 91% and 86% respectively (Koray et al., 2003). Therefore, there is still great amount of uncertainty in the application of ^{99m}Tc-MIBI imaging in the diagnosis of thyroid cancer.

^{201}Tl is a type of tumor imaging agent. Researches using quantitatively analysis of ^{201}Tl imaging data to differentiate BTN and MTN have shown that the ratio of counts between tumor and normal tissue (T/N), the ratio of counts between tumor and soft tissue (T/S) were all significantly higher in MTN than BTN. However, these results have yet to be confirmed in later research (Kumi et al., 2003).

Our study is different from above mentioned studies. We combined the data from conventional thyroid flow imaging and static imaging, and for the first time conducted quantitative analysis of these data to differentiate BTN and MTN. To our best knowledge, this has yet to be reported before. Our results also showed relatively high sensitivity and specificity for this approach. The plausible explanation might be that he growth of malignant tumors is essentially dependent on adequate blood supply. With the formation of irregular blood vessels and a gradual increase in the arteriovenous shunt, angiogenesis is the character of many types of tumor. Therefore, the evaluation of differences on vascular markers between benign and malignant tumors can provide valuable information for the diagnosis of malignant tumor (Andrej et al., 2007). Study by Andrej et al. (2007) confirmed that compared with visual observation, quantitative analysis of perfusion parameter of malignant thyroid nodules provided valuable information in differentiating BTN and MTN. In the study CTTT, TNNB/TB and TNB/CAB are all markers reflecting thyroid blood flow perfusion level, and shown to be significantly different between BTN and MTN.

Thyroid static imaging mainly measures the functional status of thyroid nodules, which can then indirectly reflects the malignancy of the nodules. Cool and cold nodules typically have high possibility of malignancy due to poor tissue differentiation or reduced function. In this study, TN/T from static imaging is a marker indicating the functional status of the nodules. The results also showed that the TN/T was significantly lower in MTN group than BTN group.

In addition, this study selected the best thresholds using ROC methodology for all 4 markers (CTTT, TNB/TB, TNB/CAB and TN/T) that have been shown to be different between MTN and BTN groups. Using the selected thresholds, we combined TN/T with CTTT, TNB/TB and TNB/CAB to evaluate the performance in differentiation diagnosis of thyroid nodule. Compared with the results of pathology exam, sensitivity, specificity, and accuracy were all relatively high when TN/T was combined with CTTT and TNB / TB together or separately.

Correlation analysis demonstrated a significant negative correlation between TN/T and TNB/TB or TNB/CAB in group of MTN. But in group of BTN, there were no apparent correlation between TN/T and CTTT , TNB/TB or TNB/CAB. This result suggests that the negative correlation between TN/T and TNB/TB or TNB/CAB can play an important role in differential thyroid nodules.

The main limitation of this study was small number of MTN cases. Therefore, the result of this study needs to be confirmed in future study with larger sample size.

In summary, combined quantitative analysis of thyroid blood flow imaging and static imaging data can provide valuable information for the differential diagnosis of benign and malignant thyroid nodules, which is critical in guiding the treatment selection and determining the patients' prognosis.

Acknowledgements

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