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Original Article

Impact of real-time contrast-enhanced ultrasound on thyroid function in microwave ablation treatment of thyroid tumors

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Abstract: Objective: To investigate the impact of contrast-enhanced ultrasound on the efficacy of microwave ablation in the treatment of benign thyroid tumors, as well as its effect on thyroid function, to assess its application value. Methods: We retrospectively analyzed data from 60 patients with benign thyroid nodules treated at Sichuan Provincial People's Hospital from January 2021 to December 2021. All patients underwent microwave ablation. Based on the intraoperative assessment of the ablation effect, they were divided into a contrast-enhanced ultrasound group (n=34) and a conventional ultrasound group (n=26). Postoperatively, the treatment outcomes were classified into complete ablation or the presence of residual nodules. We also assessed the recurrence rate one year after treatment, along with inflammatory factors, stress response indicators, and effects on thyroid function. Results: The complete ablation rate for thyroid nodules in the contrast-enhanced ultrasound group was significantly higher than that in the conventional ultrasound group (P<0.05). Intraoperative measurements revealed lower ablated nodule volumes, bleeding volumes, and in situ replacement rates in the contrast-enhanced ultrasound group, with statistically significant differences (P<0.05). Preoperative thyroid function hormone indicators, inflammatory factors and stress response indicators did not significantly differ between the two groups. Postoperatively, both groups had lower levels of free triiodothyronine (FT3) and free thyroxine (FT4), along with higher levels of thyroid-stimulating hormone (TSH), white blood cells (WBC), serum C-reactive protein (CRP), interleukin-6 (IL-6), norepinephrine (NE), epinephrine (E), and cortisol (Cor) compared to preoperative levels. However, the contrast-enhanced ultrasound group demonstrated higher FT3 and FT4 levels and lower WBC, serum CRP, IL-6, NE, E, Cor and TSH levels than the conventional ultrasound group, with statistically significant differences (all P<0.05). No statistically significant differences in complication rates were observed between the two groups. Conclusion: Contrast-enhanced ultrasound in microwave ablation for benign thyroid nodules can improve the complete ablation rate, reduce recurrence, and have a minimal impact on thyroid function, without increasing complication rates. It is recommended for clinical use.

Keywords: Real-time contrast-enhanced ultrasound, microwave ablation, thyroid nodules, thyroid function, complications

Introduction

Thyroid nodules are defined as the presence of one or more cystic, solid, or mixed formations within the thyroid gland, with most being benign [1-3]. Nevertheless, the occurrence of benign thyroid nodules has raised significant concern within the medical community and the public due to their potential to cause thyroid dysfunction, impact patients' quality of life, and pose a certain risk of malignancy. Epidemiological studies indicate a rising incidence of benign thyroid nodules, particularly in highly industrialized regions, where over half of adults may exhibit nodules detected by ultrasound [4, 5]. It is currently believed that the occurrence of

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benign thyroid nodules is influenced by environmental factors and lifestyle changes [6]. Moreover, advancements in medical technology and the prevalence of thyroid disease screenings have led to the diagnosis of previously undetected thyroid nodules, thereby increasing detection rates.

Microwave ablation has become an effective treatment for benign thyroid nodules, offering several advantages [7]. It offers high precision, allowing for accurate localization and treatment while minimizing damage to the surrounding thyroid tissue. The procedure is relatively simple, often performed under local anesthesia with a short duration and good patient tolerance. Additionally, patients typically experience a brief recovery period, enabling a quick return to normal activities and significantly improving their quality of life. Compared to traditional surgical methods, microwave ablation is associated with fewer complications and side effects, making it a safer treatment option for patients [8].

Currently, microwave ablation primarily relies on ultrasound guidance, including conventional two-dimensional ultrasound and contrast-enhanced ultrasound techniques. Conventional ultrasound is mainly used to evaluate the location, size and shape of thyroid nodules while facilitating intraoperative localization. In contrast, contrast-enhanced ultrasound technology enhances the accuracy of tumor localization, reduces the volume of thyroid tissue removed, minimizes bleeding, and alters relevant serological markers, thus improving clinical outcomes [9]. Studies have shown that contrast-enhanced ultrasound technology not only accurately visualizes thyroid and surrounding tissues but also differentiates between cystic and solid nodules, effectively reflecting blood perfusion in thyroid tissue and nodules, as supported by numerous studies. However, the clinical efficacy of contrast-enhanced ultrasound has not yet been uniformly established [10]. Therefore, this study aims to analyze the baseline data from our center to provide more evidence-based insights into the efficacy of contrast-enhanced ultrasound in the microwave ablation of thyroid nodules.

General data and methods

General data

This retrospective study included sixty patients with benign thyroid nodules who were treated at Sichuan Provincial People's Hospital from January 2021 to December 2021. All patients underwent microwave ablation and were subsequently divided into two groups based on intraoperative assessment of the ablation effect: the contrast-enhanced ultrasound group (n=34) and the conventional ultrasound group (n=26). This study was approved by the Ethics Committee of Sichuan Provincial People's Hospital.

Sample size calculation

The sample size for this study was calculated based on a parallel design with equal allocation (1:1) into a conventional ultrasound group and a contrast-enhanced ultrasound group. According to studies of similar design, the postoperative TSH values were μ1=3.73 for the conventional ultrasound group and μ2=3.03 for the contrast-enhanced ultrasound group. Anticipating a 10% dropout rate, and assuming a significance level (α) of 0.05 with a power (1-β) of 80%, we estimated the required sample size. According to the design of this clinical trial study and the primary efficacy outcome indicators, the sample size was calculated using the following formula:

$$n1 = n2 = \frac{2\,(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times \sigma^2}{(\mu 1 - \mu 2)^2}$$

Where, μ1=3.73, μ2=3.03, σ=1, α=0.05, β=0.2. Substituting these values into the equation, we determined that n1=n2=10 cases were required, yielding a minimum sample size of 20. To enhance the reliability of the findings, we included all eligible patients during the study period, resulting in a total of 60 cases [9].

Inclusion criteria

1) Patients with single unilateral nodules; 2) Patients with benign lesions confirmed by preoperative pathological puncture [11]; 3) Patients receiving treatment for thyroid nodules for the first time; 4) Patients with complete standard medical records, including current and past medical history, as well as complete preoperative laboratory and imaging results; 5) Patients aged 18-80 years.

Exclusion criteria

1) Patients with Hashimoto's thyroiditis or autoimmune thyroiditis; 2) Patients with contraindi-

cations to puncture procedures; 3) Patients with abnormalities in blood or coagulation function; 4) Patients with severe cardiac or renal insufficiency; 5) Patients with incomplete clinical data.

Treatment methods

In this study, we used the Hitachi ARIETTA70 digital ultrasonic diagnostic system, which is equipped with contrast-enhanced capabilities. The microwave ablation system was manufactured by Nanjing Great Wall Medical Equipment Co., Ltd. (China), model MTI-5DT. The intraoperative contrast agent used was SonoVue (Bracco, Italy). The specific procedure was as follows: Ablation treatments for both groups were performed by senior, professionally trained physicians. After routine local disinfection of the neck, the spatial relationship between the nodule and the recurrent laryngeal nerve or major cervical blood vessels was identified under ultrasound guidance. Physiological saline was injected to create a liquid barrier between the thyroid nodule and these critical structures, minimizing the risk of injury during the procedure.

Following these steps, the microwave needle was inserted into the thyroid nodule under ultrasound guidance, and the ablation device was activated with a power setting of 30-50 watts. For larger nodules, a combination of multipoint, multiplane, moving, and fixed-point ablation techniques was employed. This approach often results in postoperative ultrasound showing hyperechoic phenomena within the thyroid nodules. For the contrast-enhanced ultrasound group, contrast-enhanced ultrasound was performed preoperatively to determine the size, location, and blood flow of the nodules. After a slight reduction in echogenicity, a second ultrasound enhancement was performed. Complete ablation was indicated by the absence of contrast agent perfusion in the target area. Conversely, the conventional ultrasound group underwent conventional ultrasound-guided ablation therapy. Treatment was considered complete when color Doppler flow imaging (CDFI) showed no detectable blood flow signals in the target area [11, 12].

Primary observational indicators

The primary observational indicators included complete nodule ablation rate of nodules, nodule volume reduction, bleeding volume, in situ recurrence rate, and changes in thyroid function before and after treatment (measured by thyroid-stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) levels). To assess these indicators, 3 ml of fasting venous blood was collected from all patients at 7:00 am on the second day following admission and after the procedure. Serum was obtained via centrifugation (3000 rpm for 10 minutes), and levels of TSH, T3, T4, FT3, and FT4 were analyzed using an automatic analyzer.

Secondary observational indicators

Secondary observational indicators included the incidence of complications in both groups and changes in stress-related hormones (norepinephrine (NE), epinephrine (E), cortisol (Cor)) levels and related inflammatory markers (tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), interleukin-6 (IL-6)) before and after treatment. The levels of IL-6, TNF-α, CRP, NE, E, and Cor were measured using a Siemens automatic biochemical analyzer (Japan). IL-6 (JM-03204H1), TNF-α (JM-03277H1), NE (JM-03-878H1), E (JM-03906H1), and Cor (JM-0393-1H1) were quantified using enzyme-linked immunosorbent assay (Shanghai Enzyme-linked Biotechnology Co., Ltd.), while CRP levels were determined by electrochemiluminescence method (Wuhan Easy Diagnosis Biomedicine Co., Ltd.).

Statistical analysis

Data analysis was conducted using SPSS 26.0 software. Measurement data were presented as mean ± SEM and were analyzed using t-tests for normally distributed data. Continuous variables with non-normal distributions were represented by median and interquartile ranges. Paired-sample t-tests were used for within-group comparisons, while independent-sample t-tests were used for between-group comparisons. For non-normally distributed data, the Mann-Whitney U test was used. Categorical data were reported as rates (percentages), with chi-square tests used for analysis. $P<0.05$ was considered statistically significant.

Results

Comparison of baseline data between the two groups

The results of this study showed no statistically significant differences between the two groups

Table 1. Comparison of general data between the two groups

Group	Contrast-enhanced ultrasound group (n=34)	Conventional ultrasound group (n=26)	t/χ^2	P
Gender (Male/Female)	11/23	12/14	0.287	0.564
Age	47.9±6.0	46.3±6.2	0.443	0.413
BMI	23.8±2.2	24.0±1.9	0.780	0.273
Hypertension	7	4	0.442	0.574
Nodule Diameter (cm)	3.2±0.2	3.1±0.2	0.232	0.574
Nodule Location (Left/Right)	12/22	10/16	0.043	0.747
Ultrasound TIRADS Classification (III/IV)	5/29	6/20	0.020	0.650
Number of lesions (Single/Multiple)	18/16	13/13	0.051	0.821
Echo Pattern (Low/Equal/Mixed)	8/12/14	13/8/5	0.112	0.954
Boundary Definition (Clear/Unclear)	15/19	11/15	0.020	0.889
Morphology (Regular/Irregular)	14/20	14/12	0.950	0.330
Vertical/Horizontal Ratio (>1/≤1)	20/14	19/7	1.326	0.251
Calcification Status (With/Without)	13/21	10/16	<0.001	0.985
Elasticity Score	3.5±1.2	3.3±1.3	0.850	0.692
Film Continuity (Continuous/Destructive)	12/22	8/18	0.138	0.713

Note: BMI: Body mass index; TIRADS: Thyroid Imaging Reporting and Data System.

Table 2. Comparison of surgery-related indicators between the two groups

Group	Contrast-enhanced ultrasound group (n=34)	Conventional ultrasound group (n=26)	t	P
Operation Time (min)	73.5±11.4	69.8±12.0	0.667	0.565
Intraoperative Blood Loss (ml)	10.9±2.8	22.8±3.4	14.443	<0.001
Hospital Stay (Days)	6.5±0.52	6.4±0.49	0.339	0.421

in terms of gender, age, body mass index, comorbidities, nodule diameter, location, and grade (all P>0.05), indicating comparability (See **Table 1**).

Comparison of intraoperative and postoperative data between the two groups

The contrast-enhanced ultrasound group had significantly less intraoperative blood loss compared to the conventional ultrasound group (P<0.001). However, there were no statistically significant differences between the two groups in terms of operation time and length of hospital stay (**Table 2**).

Comparison of complete ablation rate and intraoperative nodule ablation volume between the two groups

The complete ablation rate was higher in the contrast-enhanced ultrasound group compared to the control group (28/34 vs. 15/26, P=0.043). Additionally, the intraoperative ablation volume of thyroid nodules was smaller in the contrast-enhanced ultrasound group (P<0.001) (**Figures 1**, **2**).

Comparison of postoperative nodule in-situ recurrence rate between the two groups

The in-situ recurrence rate was lower in the contrast-enhanced ultrasound group compared to the conventional ultrasound group, and the difference was statistically significant (P=0.045) (**Figure 3**).

Comparison of inflammatory response factors before and after treatment between the two groups

Postoperatively, both groups exhibited increased levels of WBC, serum CRP, and IL-6 compared to preoperative levels, with statistically significant differences (all P<0.05). Additionally, the increases in these indicators was less pronounced in the contrast-enhanced ultrasound group compared to the conventional ultrasound group (**Figure 4**).

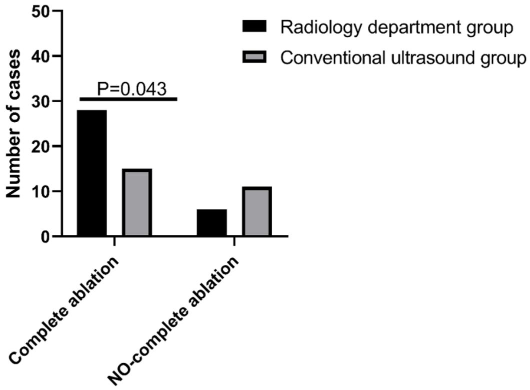

Figure 1. Comparison of complete ablation rates between the two groups.

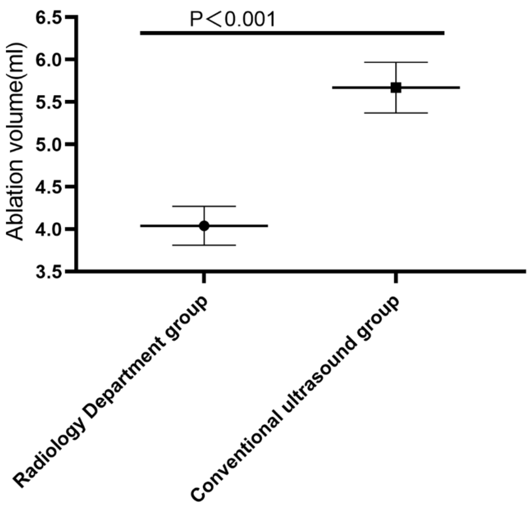

Figure 2. Comparison of intraoperative ablation volumes between the two groups.

Comparison of stress response indicators between the two groups

Postoperatively, serum levels of NE, E, and Cor increased in both groups compared to preoperative levels, with statistically significant differences (all P<0.01). Additionally, the increases in these stress response indicators were less pronounced in the contrast-enhanced ultrasound group compared to the conventional ultrasound group (**Figure 5**).

Comparison of thyroid hormones before and after surgery between the two groups

There were no statistically significant differences in serum levels of TSH, FT4, and FT3 between the two groups before surgery. Three months after treatment, both groups demonstrated lower FT3 and FT4 levels and higher TSH levels compared to preoperative values. However, the contrast-enhanced ultrasound group had significantly higher FT3 and FT4 levels and lower TSH levels compared to the conventional ultrasound group (all P<0.05) (**Figure 6**).

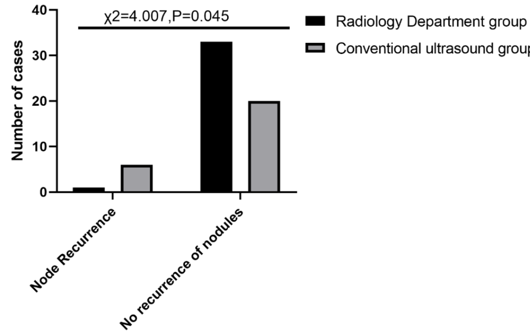

Figure 3. Comparison of postoperative in-situ recurrence rates between the two groups.

Comparison of surgical complications between the two groups

There were no statistically significant differences in the incidence of postoperative complications between the two groups (P=0.434) (**Table 3**).

Ultrasound imaging before and after ablation in the two groups

In conventional ultrasound, nodules before ablation appeared as round or oval homogeneous isoechoic lesions with clear boundaries from the surrounding tissue (**Figure 7A**). In contrast-enhanced ultrasound mode, there was no significant difference between the nodule and surrounding normal tissue prior to ablation; the nodule exhibited enhancement similar to that of normal thyroid tissue in both arterial and venous phases (**Figure 7B**). Post-ablation, conventional ultrasound showed the nodules as round or quasi-round mixed and uneven echogenic lesions with well-defined borders from the surrounding tissues (**Figure 8A**). Immediately after ablation or three months later, the ablation area showed spotty enhancement. After complete ablation, the nodules appeared as non-enhanced regions with clear boundaries from normal thyroid tissue, characterized by a "black hole" sign (**Figure 8B**).

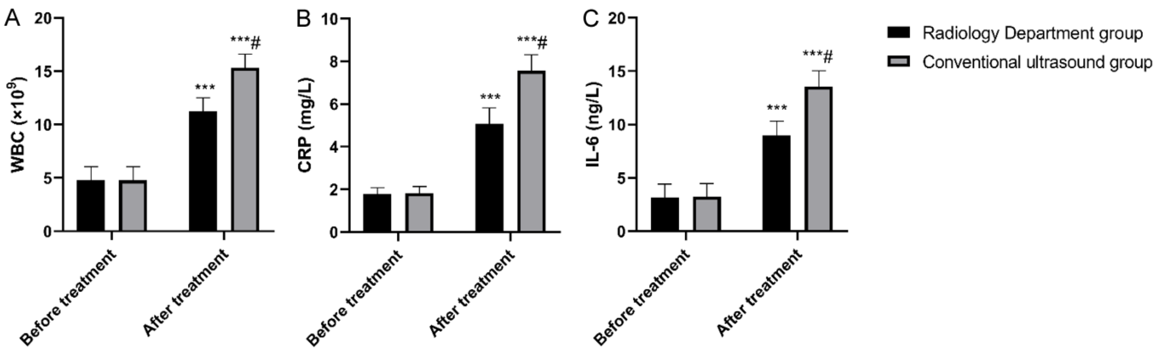

Figure 4. Comparison of inflammatory indicators before and after surgery between the two groups. A: White Blood Cell Count Before and After Surgery; B: CRP Levels Before and After Surgery; C: IL-6 Levels Before and After Surgery. ***Indicates a significant difference between preoperative and postoperative values, P<0.001; #Indicates a significant difference between the contrast-enhanced ultrasound group and the conventional ultrasound group postoperatively, P<0.05. CRP: C-reactive protein.

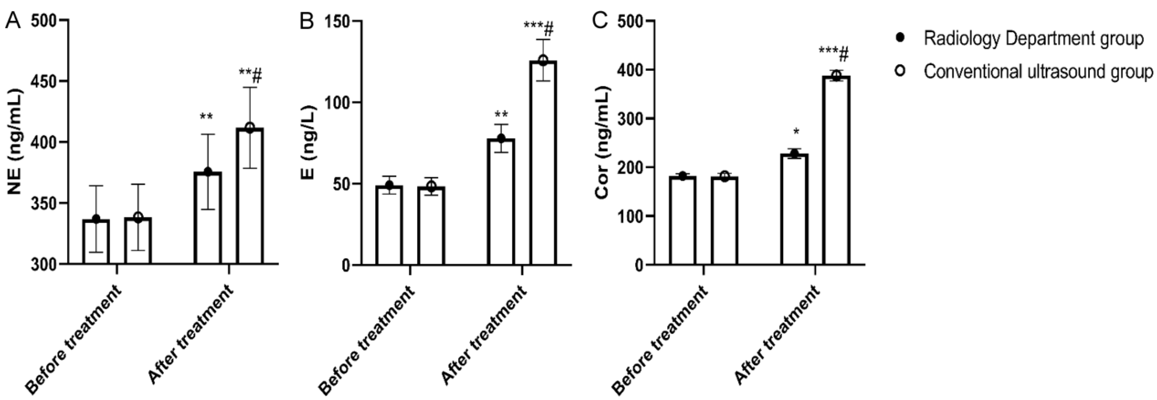

Figure 5. Comparison of stress response indicators before and after surgery between the two groups. A: NE Levels Before and After Surgery; B: E Levels Before and After Surgery; C: Cor Levels Before and After Surgery. Compared with postoperative levels, *P<0.05, **P<0.01, ***P<0.001. #Indicates a significant difference between the contrast-enhanced ultrasound group and the conventional ultrasound group postoperatively, P<0.05. NE: norepinephrine; E: epinephrine; Cor: cortisol.

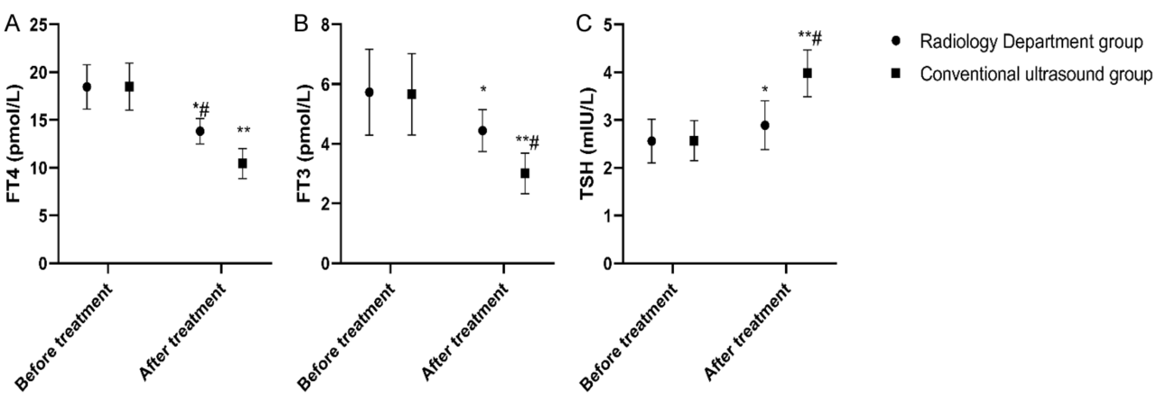

Figure 6. Comparison of thyroid function indicators before and after treatment between the two groups. A: FT4 Levels Before and After Surgery; B: FT3 Levels Before and After Surgery; C: TSH Levels Before and After Surgery. Compared with postoperative levels, *P<0.05; **P<0.01; #Indicates a significant difference between the contrast-enhanced ultrasound group and the conventional ultrasound group postoperatively, P<0.05. FT4: free thyroxine; FT3: free triiodothyronine; TSH: thyroid-stimulating hormone.

Table 3. Comparison of complication rates between the two groups

Group	Contrast-enhanced ultrasound group (n=34)	Conventional ultrasound group (n=26)	χ^2	P
Bleeding	1	1		
Incision Infection	1	2		
Nerve Damage	0	1		
Total	2/34	4/26	0.611	0.434

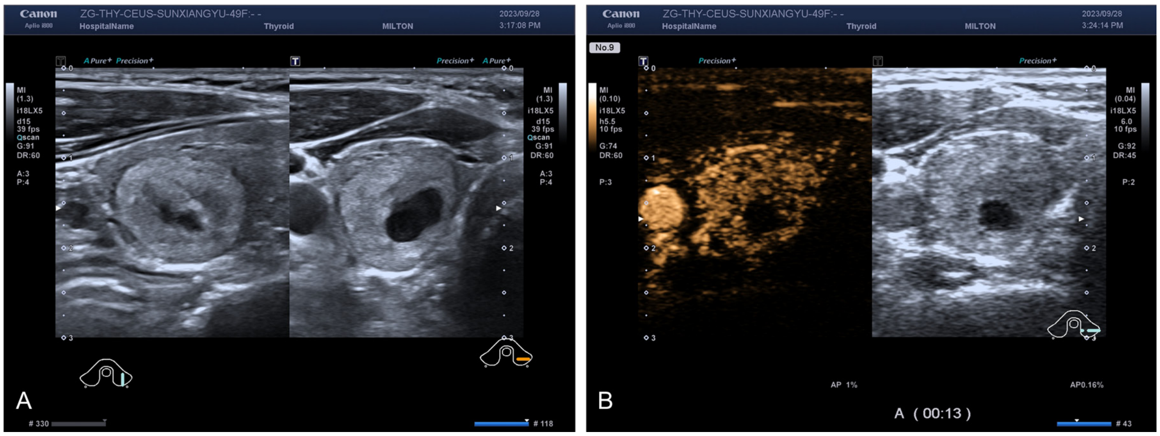

Figure 7. Conventional ultrasound and contrast imaging before ablation in the two groups. A: Conventional ultrasound image of the thyroid before ablation; B: Ultrasound imaging of thyroid gland before ablation.

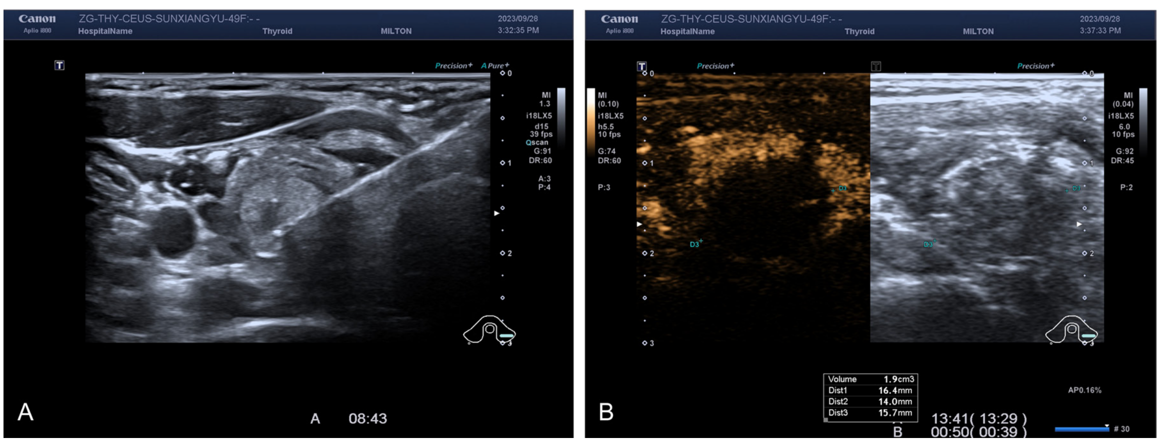

Figure 8. Ultrasound images during and after ablation of the two groups. A: Common ultrasound images of the thyroid during ablation; B: Immediate ablative thyroid CEUS. Note: CEUS: Contrast-enhanced ultrasound.

Discussion

Benign thyroid nodules are non-cancerous growths that can be single or multiple and vary in size [13, 14]. Current research confirms that most benign thyroid nodules are asymptomatic, leading many patients to remain unaware of their condition for extended periods, which can delay diagnosis and treatment [15]. However, as nodules grow, they may compress surrounding tissues, leading to symptoms such as dysphagia, dyspnea, or hoarseness. Additionally, these nodules may disrupt thyroid function, potentially causing hyperthyroidism and associated metabolic disorders [16]. Therefore, effective treatment of benign thyroid nodules is essential not only for alleviating physical discomfort but also for preventing potential health risks.

Currently, the primary approach for managing thyroid nodules is removal, with common methods including surgical excision and ablation. While surgery is effective and ensures complete removal, it often involves large incisions, unsatisfactory cosmetic outcomes, and risks to thyroid function. Consequently, more patients opt for minimally invasive treatments like microwave ablation, which has shown promising results in clinical practice [17, 18]. Microwave ablation is an innovative, non-surgical therapy that employs the thermal effects of microwave energy to target the nodule tissue directly, inducing coagulative necrosis and effectively eliminating the nodule. This method has significant advantages, including minimal trauma, rapid recovery, and fewer side effects, making it particularly suitable for patients who may not tolerate traditional surgery due to age, physical condition, or other diseases. The mechanism of microwave ablation involves delivering microwave radiation at specific frequencies that penetrate the skin to act directly on the thyroid nodule. This radiation causes water molecules within the nodule to vibrate rapidly, generating heat that leads to coagulative necrosis of the nodule tissue at high temperatures. Importantly, this process not only effectively eliminates the nodule but also maximally protects the surrounding healthy thyroid tissue and critical neck structures, such as the vocal cords and parathyroid glands, minimizing the trauma and complications often associated with traditional surgery. Moreover, microwave ablation is a straightforward procedure that typically requires no general anesthesia and can be completed within half an hour, allowing patients to return to normal activities almost immediately without prolonged hospitalization. Thus, microwave ablation has become a preferred treatment method for benign thyroid nodules [19, 20].

Currently, microwave ablation relies on ultrasound guidance; however, conventional ultrasound has notable limitations, such as poor visualization of the vascularity of thyroid nodules and relatively inaccurate delineation of tissue boundaries. Contrast-enhanced ultrasound addresses these shortcomings [21]. Previous studies have shown that contrast-enhanced ultrasound can improve the clinical effectiveness of nodule treatments. Our findings indicate that the complete ablation rate of thyroid nodules in the contrast-enhanced ultrasound group was significantly higher than that in the conventional ultrasound group. Moreover, the contrast-enhanced ultrasound group had smaller ablation volumes, reduced bleeding, and a lower in-situ recurrence rate during the procedure. The underlying mechanisms for these improvements are multifaceted. Contrast-enhanced ultrasound provides clear visualization of nodule boundaries and tissue perfusion, thereby improving intraoperative guidance and surgical precision, which reduces the likelihood of residual nodules. Furthermore, it is more resilient to interference within the ablation zone and can sensitively detect blood flow in residual nodules, leading to fewer punctures and reduced intraoperative bleeding in the contrast-enhanced ultrasound group. The discrepancies in nodule volume changes between the two groups can be attributed to conventional ultrasound's limited ability to clearly delineate the ablation area post-procedure, which often results in indistinct nodule boundaries and heterogeneous internal echoes. In contrast, contrast-enhanced ultrasound can effectively display changes in the ablation area, facilitating the re-ablation of residual nodules, minimizing residual lesions, and ultimately reducing the in-situ recurrence rate. These findings align with conclusions from previous studies [22, 23].

Studies have indicated that thyroidectomy has a certain impact on thyroid hormone levels, with the procedure itself potentially elevating indicators related to stress response (NE, E, Cor) and inflammatory response (WBC, CRP, IL-6) [24]. In our study, both groups experienced varying degrees of thyroid function impairment after surgery, characterized by significantly increased TSH levels and decreased FT4 and FT3 levels. However, the ablation group demonstrated better preservation of thyroid function compared to the traditional surgery group. Furthermore, inflammatory markers and stress response indicators were lower in the contrast-enhanced ultrasound group compared to the conventional ultrasound group. This suggests that microwave ablation, when combined with contrast-enhanced ultrasound, may better protect thyroid function while reducing inflammation and stress responses. This can be attributed to several factors: the enhanced efficacy of nodule removal with contrast-enhanced ultrasound minimizes the extent of thyroid tissue resection and the number of punctures, thereby reducing thermal damage to surrounding healthy tissues. This protective effect helps preserve thyroid tissues and function, consequently lowering surgical stress and the associated inflammatory response. Similar findings have been reported in previous studies [25].

When comparing the incidence of surgical complications between the two groups, no statistically significant differences were found. The complications were primarily common in nature, with no novel complications observed. This is mainly because contrast-enhanced ultrasound does not increase the overall complexity of the ablation procedure. These findings further confirm the safety of microwave ablation and reinforce previous research conclusions [26].

In conclusion, contrast-enhanced ultrasound combined with microwave ablation for the treatment of nodular goiter can reduce intraoperative bleeding, diminish postoperative stress and inflammatory response, and minimize damage to thyroid function, all without increasing the incidence of adverse reactions. This approach demonstrates a favorable safety profile and is recommended for clinical application. However, it is important to note that this study is limited by its single-center design and relatively small sample size. Future large-sample, multi-center studies are needed to validate the clinical efficacy of contrast-enhanced ultrasound-guided minimally invasive ablation in thyroidectomy. Additionally, establishing objective surgical indications for microwave ablation and incorporating more serum biomarkers for evaluating ablation effectiveness can further strengthen the conclusions drawn from this study.

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Disclosure of conflict of interest

None.

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