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Original Article

Ultrasonography-guided radiofrequency ablation combined with lauromacrogol sclerotherapy for mixed thyroid nodules

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Abstract: Objective: To evaluate the safety and effectiveness of ultrasonography-guided radiofrequency ablation combined with lauromacrogol foam sclerotherapy for the treatment of mixed thyroid nodules. Methods: One hundred and nineteen patients with benign mixed thyroid nodules were included in this study. In all patients, radiofrequency ablation was performed on the solid components of nodules, and the cystic areas of nodules were treated with aspiration, irrigation with lauromacrogol injection and foam sclerotherapy. The nodule volume reduction ratio and thyroid-related laboratory tests were measured during operation and at 1, 3, 6, and 12 months after operation, and intraoperative and postoperative complications were recorded. Results: A total of 136 mixed thyroid nodules from 119 patients all achieved complete ablation. At 1, 3, 6, and 12 months after treatment, the nodule volume decreased gradually while the volume reduction ratio increased gradually ($P<0.05$). The thyroid function of all patients returned to normal after operation, but 3 patients exhibited cyst recurrence. After the operation, no serious complications occurred. Conclusion: Ultrasonography-guided radiofrequency ablation combined with lauromacrogol sclerotherapy is a safe and effective method for the treatment of mixed thyroid nodules with less surgical trauma and low incidence of complications.

Keywords: Thyroid nodule, radiofrequency ablation, lauromacrogol, sclerotherapy

Introduction

Most thyroid nodules are benign. Of all benign nodules, mixed nodules are important components [1]. The majority of mixed nodules are nodular goiter, also known as glial nodules, which are caused by the degeneration, extensive liquefaction, and bleeding of hyperplastic nodules. Some of them are caused by the cystic changes of follicular adenoma while mixed nodules caused by the liquefaction of papillary carcinoma are relatively rare [2]. Most mixed nodules are large in size, with some protruding subcutaneously. The rapid enlargement of nodules may cause the compression of important anatomical structures such as the trachea, esophagus, and large vessels in the neck, which can cause choking sensations during swallowing and foreign body sensation in the throat. In addition, it can affect ventilation [3]. For thyroid nodules, the traditional treatment is subtotal thyroidectomy. However, it is difficult to avoid various intraoperative and postoperative complications, such as injury of the superior laryngeal nerve and recurrent laryngeal nerve (0.8%-9.5%), abnormalities in thyroid function occur due to the removal of most glands (4%-6%), and neck scars occur (8%-11%) [4, 5].

In recent years, radiofrequency ablation (RFA) and chemical sclerotherapy have been widely applied in the treatment of thyroid nodules [6]. Chemical ablation is often used for simple thyroid cystic lesions, which is currently 95% ethanol or lauromacrogol injection as the main ablation agents. However, pure anhydrous ethanol

is well diffused, easily spilled and difficult to control the extent of ablation [7, 8]. Lauromacrogol injection consists of 90% anhydrous alcohol and 10% polyoxyethylene lauryl ether, having the effect of cell dehydration and tissue fibrosis, which is better than anhydrous ethanol on the effect of ablation [9]. RFA is a treatment method that utilizes high-frequency oscillating current (usually 200-750 kHz, less than 100 W) generated by a radio frequency generator. By transferring the electrical energy through a needle electrode to the target area, this method can cause the vibration and friction between polar molecules and ions in its surrounding tissues. Then the energy generated by vibration and friction is converted into thermal energy, leading to irreversible thermal coagulation and necrosis of proteins in local tissues and cells. Finally, local focus inactivation can be achieved with the absorption of necrotic tissue [10]. Having the advantages of being less invasive, quicker, shorter, safer and more reliable, RFA has gradually matured in the treatment of benign and malignant tumors of the liver, lung and kidney, and much attention has been focused on the treatment of thyroid nodules by RFA [11-13]. Previous studies have reported the application value of RFA in patients with thyroid nodules. By comparing conventional surgery, they found that the treatment efficiency and quality of survival were significantly higher in the radiofrequency ablation group than those in the conventional surgery group, while the incidence of adverse effects was significantly lower than that in the conventional surgery group [14].

However, in the treatment of mixed thyroid nodules, the combination of radiofrequency ablation and chemical sclerosis is less commonly used, so the efficacy of combined therapy for mixed thyroid nodules is unclear [15]. In this study, radiofrequency ablation combined with lauromacrogol sclerotherapy was applied to treat mixed thyroid nodules with the aim to evaluate the clinical value of combined therapy in the treatment of mixed thyroid nodules.

Materials and methods

General information

A prospective study was conducted in 119 patients with mixed thyroid nodules in our hospital from October 2017 to December 2019. There were 42 males and 77 females aged from 18 to 82 years with an average of (49.6±12.2).

Inclusion criteria: Preoperative ultrasonography showed mixed thyroid nodules without malignant signs; fine needle aspiration cytology (FNAC) did not reveal malignant pathology; all relevant laboratory tests (including complete blood cell count, coagulation function, thyroid function, thyroid-associated antibodies, and calcitonin) were within the normal range before operation; patients who had refused routine surgical treatment and were ready to receive combined therapy of radiofrequency ablation and chemical sclerosis.

Exclusion criteria: Electronic laryngoscope showed contralateral vocal cord dysfunction; patients with severe coagulation dysfunction; patients combined with severe primary diseases such as cardiovascular disease or other serious infectious diseases; pregnant and lactating women [16].

All patients and their families signed the informed consent, and this study was approved by the Ethics Committee of our hospital.

Equipment and methods

Equipment: Color doppler ultrasound: Color Doppler ultrasonic diagnostic apparatus (Esaote, MyLabTMTwice, Italy) with LA523 probe and a probe frequency of 5-12 MHz. Ablation system: Radiofrequency ablation generator (model S-5L, MedSphere International, Inc., Shanghai, China) with the operating frequency of 480 KHz (455-490 KHz), 19 G water-cooled radiofrequency (WC-RF) ablation electrode (d = 3 mm). Ultrasonography contrast agent: injection of a sulphur hexafluoride microbubble agent (Bracco Suisse SA Company, Italy); lauromacrogol hardener (Shanxi Tianyu Pharmaceutical Co., Ltd., China).

Methods: The patients were placed in a supine position with the neck hyper-extended and fully exposed. The venous access was established and all vital parameters were monitored. Total intravenous anesthesia was administered with 5 mg Dezocine (Yangzi River Pharmaceuticals Group Co., Ltd., China) and 0.0015-0.002 mg/kg body weight Fentanyl (Yichang Renfu Pharmaceutical Co., Ltd.,

China). The neck was disinfected and padded with a sterile surgical towel. Then ultrasound examination was performed to fully understand the conditions of nodules and adjacent organs. After this, the puncture location and pathway were planned. Contrast-enhanced ultrasonography was performed to determine whether the solid components within the nodules were enhanced.

Under ultrasonographic guidance, a 6Fr coaxial trocar was placed in the cystic portion of the nodule, and a pig-tail catheter was inserted. The cyst fluid was drawn out and the total volume of cyst fluid was recorded. The cyst cavity was washed 3-5 times rapidly using sterile saline solution after drawing out the cyst fluid. If the cyst fluid was composed of a colloid component, then the number of times of displacement flushings was increased until the liquid component in the cystic cavity was replaced completely and could be drawn out entirely. Next, the lauromacrogol injection (approximately 1/4-1/3 of the fluid extracted from the cystic cavity up to a maximum of 35 mL) was slowly injected into the cystic cavity to wash the cyst wall repeatedly. The lauromacrogol injection was temporarily left in the cyst cavity after washing for 5 min (**Figure 1**). Sterile normal saline was instilled into the fascial sheath of the thyroid with ultrasound guidance. The liquid separation was formed by separating the thyroid from its surrounding tissues to prevent heat damage to surrounding organs and tissues during ablation. The RFA needle electrode was inserted into the solid and contrast-enhancing components of nodules under ultrasound guidance with the emission power of 20 W. Multi-point mobile ablation, layer by layer was then performed to completely cover the solid components of nodules especially near the capsule of nodules. The ablative zone appeared hyperechoic on ultrasound. The contrast enhanced area was the focus area. Patients were left for observation after the ablation was completed. After all ablation bubbles dissipated, contrast-enhanced ultrasonography was performed to evaluate the efficacy of RFA in real time. The nodule was considered as completely ablated if the preoperative contrast-enhanced areas showed no enhancement and 'cavity sign' (**Figure 2**). All the liquid components were drawn out by the indwelling catheter after ablation. Then lauromacrogol and air (1:1) foam agent was injected into the cyst cavity until the foam was completely diffused. Cold compresses were applied locally for 1 h after ablation.

Postoperative follow-up evaluation

Intraoperative complications such as intraoperative bleeding and recrudescence of cystic cavity as well as postoperative complications such as hematoma, infection, and an abnormal voice were recorded promptly following surgery. In addition, all patients returned for routine echocardiography and relevant laboratory tests at 1, 3, 6, and 12 months postoperatively. Also, a contrast-enhanced ultrasound examination was performed at 3 months postoperatively to observe the nodule size and measure the nodule volume ($V = \pi abc/6$, a, b, and c represent maximum diameter, transverse diameter and longitudinal diameter, respectively). The volume reduction ratio (VRR) at different time points was calculated. VRR = (Vpreoperation - Vreview)/Vpreoperation. Meanwhile, the echoes of ablative areas and changes of blood flow signals were observed.

Statistical analysis

SPSS Statistics 22.0 was used for statistical analysis. The volume and VRR of nodules were measurement data meeting a normal distribution and were expressed as mean ± standard deviation ($\bar{x} \pm sd$). One-way repeated measures analysis of variance (ANOVA) was used for comparison between VRR at 1, 3, 6, and 12 months after ablation. $P<0.05$ was considered statistically significant.

Results

Changes in nodule volume at different time points after operation

In this study, a total of 136 mixed nodules were evaluated during operation by contrast-enhanced ultrasound in 119 patients. Under ultrasound, the solid enhancing components were all completely ablated and destroyed, and the contrast-enhanced ultrasound demonstrated the 'cavity sign'. The nodule volume progressively decreased at 1, 3, 6, and 12 months after treatment. Analysis was performed using one-way repeated measurement.

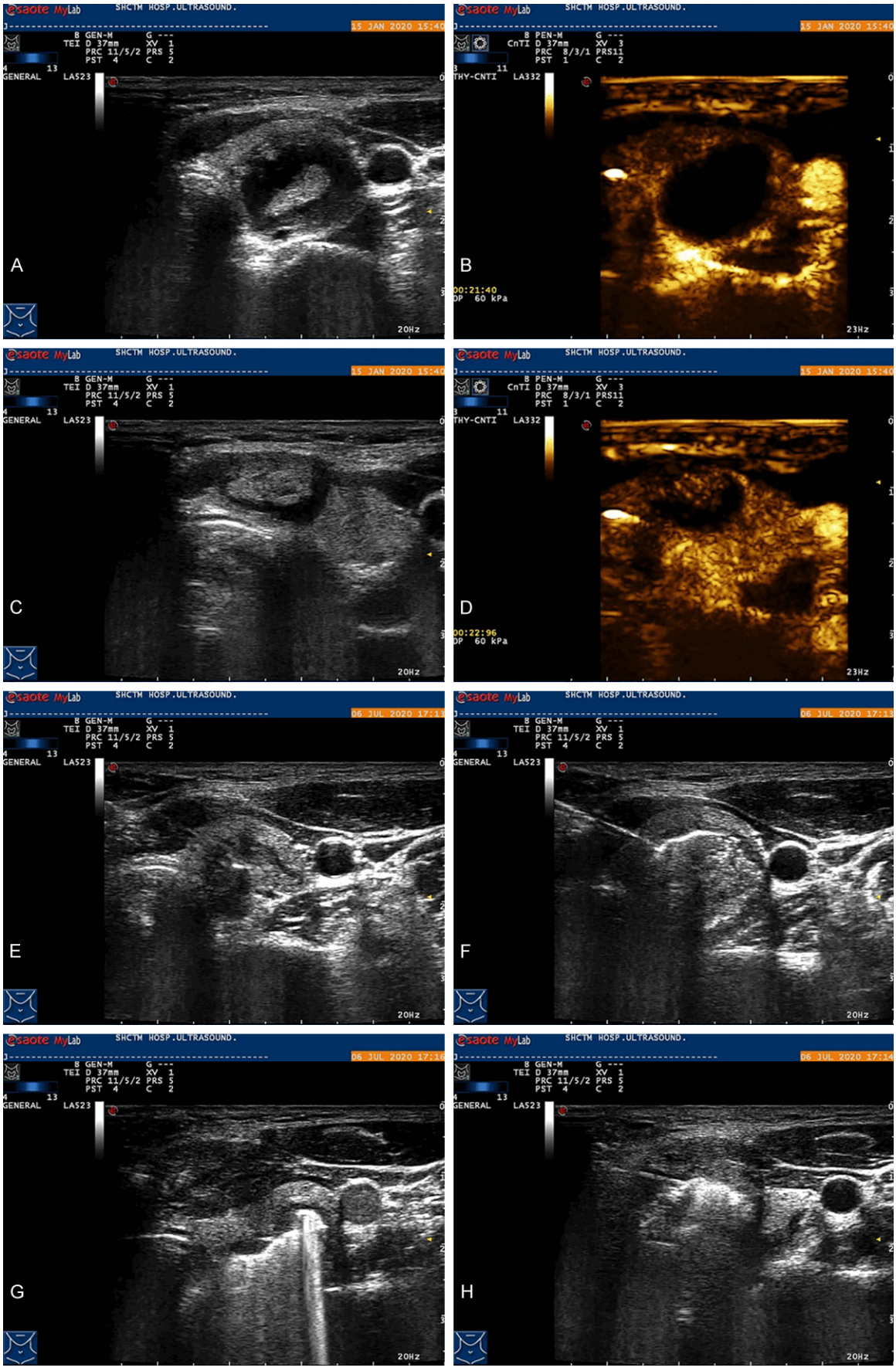
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Figure 1. Ultrasonography-guided ablation combined with sclerotherapy for mixed thyroid nodules. A and C: Solid components visible in different locations of the same mixed nodule; B and D: Preoperative angiography revealed enhancing changes in some solid components; E: Cyst cavity without cyst fluid; F: A liquid dark area filling the cyst cavity was observed after injection of sclerosing agent for lavage; G: A bright hyperechoic region was observed accompanied by a lot of multiple reflections after injection of foam agent; H: RFA was performed for the solid components with contrast enhancement.

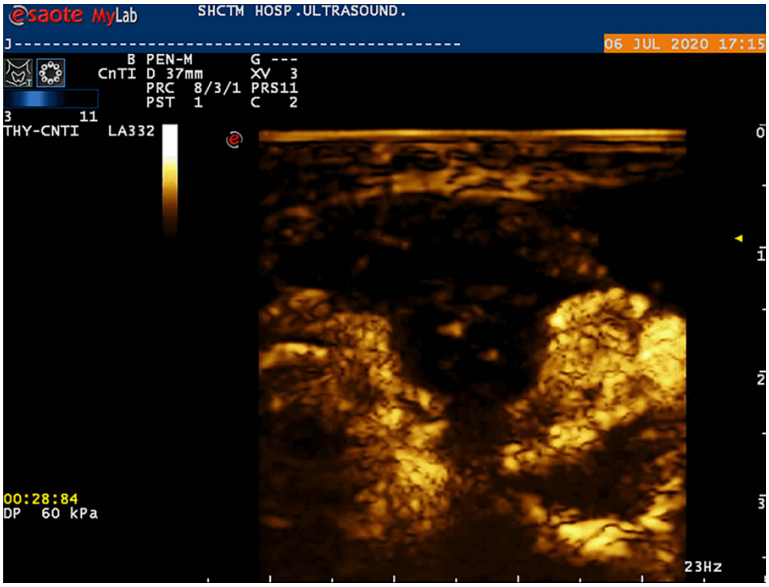

Figure 2. The solid components of the nodules showed the 'cavity sign' with no enhancement after contrast-enhanced ultrasonography.

Table 1. Changes in nodule volume and VRR

	Vmean (mL)	VRR (%)
Preoperation	12.55±3.95	
One month after operation	9.35±6.21*	25.88±13.21
Three months after operation	8.52±4.59*,#	31.75±5.63#
Six months after operation	4.43±2.11*,#	64.71±1.71#
Twelve months after operation	1.12±0.61*,#	91.08±0.05#

Note: Compared with pre-operation, *P<0.05; compared with previous review, #P<0.05.

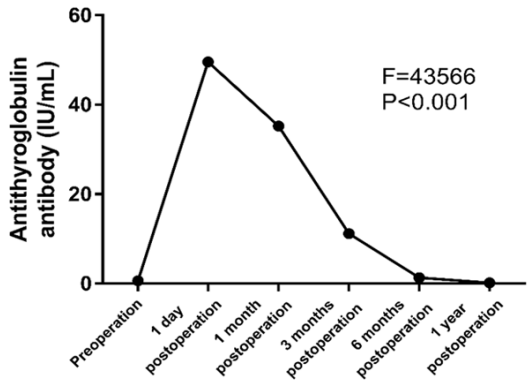

Figure 3. Change in the level of antithyroglobulin antibody over time.

As shown in **Table 1**, the results showed that the nodule volume decreased significantly at different time points after operation compared with that before operation (P<0.05), and VRR increased significantly over time after operation (P<0.05). At the 12th month of follow-up, 3 patients exhibited cyst recurrence.

Changes in serum indicators related to thyroid function before and after operation

The serum free triiodothyronine (FT3), serum free tetraiodothyronine (FT4), and thyroid stimulating hormone (TSH) in all patients were within the normal range before treatment and after operation. After operation, the level of antithyroglobulin antibody (TgAb) increased transiently, reaching a peak on the first postoperative day and decreasing rapidly, returning to almost normal at the 6th month. See **Figure 3**.

Intraoperative and postoperative complications

In this study, intraoperative intracystic hemorrhage was observed in 6 patients with an average volume of 5.50±2.10 mL (depending on the final extraction volume). Recurrence of cystic cavity was observed in 3 patients at the 12th month of review with the mean recurrence volume accounting for 27.00%±5.00% of preoperative volume. The cystic cavity appeared anechoic with punctate weak echoes in the ultrasonography, and spontaneous bleeding was observed through puncture again. Of all 119 patients, none of them developed postoperative hematoma and bleeding, infection, as

Table 2. Related complications

Complications	Number (case)
Intraoperative intracystic hemorrhage	6
Recurrence of cystic cavity	3
Postoperative hematoma	0
Postoperative infection	0
Hoarseness	0
Cough	0

well as hoarseness and cough caused by nerve injuries. See **Table 2**.

Discussion

A Mixed thyroid nodule is also known as cystic-solid nodule, and the early stage of which may be asymptomatic. With the enlargement of nodules, the patients can present with symptoms such as neck mass and dysphagia. If the mixed nodule is large, rapidly growing, with significant calcification and poorly defined, surgery is likely required. With the development of imaging technology, more and more thyroid nodules have been found each year, so it is especially important to choose the appropriate treatment [17]. According to the literature, chemical ablation has been successfully applied to treating single cystic thyroid nodules. However, the efficacy of the treatment for mixed nodules has been inconsistent. Multiple studies have shown that the treatment by thermal ablation is more effective than that by simple chemical ablation for treating mixed thyroid nodules [18].

Lauromacrogol injection contains polyoxyethylene lauryl ether, which is the least irritating surfactant available for tissues. It not only can reduce the irritation of ethanol and promote fibrosis, but also has a good foaming property and can be used to prepare foam. In this study, air and lauromacrogol (1:1) foam agent was used. The air and lauromacrogol were mixed fully in a syringe to form a fine and stable foam with strong adhesion. Meanwhile, the volume of the hardener was increased, which can achieve good cystic cavity filling at the lowest possible dose and has the effect of persistent sclerosis and inducing adhesion of the cyst wall. Overall, the therapeutic effect of air and lauromacrogol foam agent is significantly better than that of simple liquid sclerosis [19, 20]. In addition, a large number of clinical studies have reported the efficacy of microwave ablation for benign thyroid nodules. However, there were some risks of complications for a variety of reasons [21-23].

According to the structural characteristics of the mixed nodules, in this study, the solid components of the nodules were destroyed by RFA, and the cystic components were destroyed by lauromacrogol irrigation and foam agent retention. The aim of this study was to find a perfect treatment schedule for mixed thyroid nodules.

In this study, the solid and contrast-enhancing components in the mixed nodules were considered to be follicular components with capillary beds. The solid components all achieved a complete ablation during operation. Intensive ablation was performed in the regions where vessels enter into the tumor. The cystic area is then treated in a sequence of aspiration, flushing and sclerosis to close the cyst cavity as much as possible. After the operation, we found that the change of VRR was the biggest in the first month, which was caused by the reactive exudation of cystic cavity after partial nodular sclerosis. With the absorption of reactive exudation and re-closure of the cystic cavity, the solid components began to shrink. At the third month, VRR was close to 1/3. With the absorption of necrotic tissues in the solid components, VRR achieved a satisfactory level. However, the cystic cavity damage still had the potential for spontaneous bleeding, which was the main cause of recurrence in 3 cases, but none of them recurred after fluid withdrawal and re-hardening. The results in our study were similar to the follow-up results of 6-12 months in other literature after ablation of benign thyroid nodules. Compared with conventional surgery, the combination therapy has the advantages of less intraoperative bleeding, fewer postoperative complications, and lower recurrence rate, which indicates that the combination of RFA and lauromacrogol foam sclerotherapy has a good clinical effects [24, 25].

In this study, after postoperative follow-up of one year, we found that there was no significant difference in the indicators related to thyroid function except TgAb, indicating that microwave ablation had no damage to the thyroid function. The change curve of TgAb indicated that the follicular cells and residual follicles in the nodules

were destroyed by thermal ablation, and the contents of the cells were released into the blood, which triggered a certain degree of immune response. Therefore, the level of TgAb peaked on the first day after operation, decreased gradually, and returned to almost normal after 6 months. TgAb remained at a low level due to the limited destruction of normal gland tissues [26].

In this study, there was a small amount of bleeding during the operation, which was mainly caused by the insertion of a coaxial trocar. The needle of coaxial trocar was a little thicker than that of the syringe. This allowed a pig-tail catheter to be placed with a side hole, so the catheter was difficult to be blocked by the viscous component in the cystic fluid. Although the puncture wound was slightly larger, indwelling flexible catheter did not cause secondary damage to the cyst wall. Moreover, the liquid diffusion effect of puncture needle with multiple holes was better than that with a single hole. Overall, the needle of coaxial trocar was better than the rigid needle in terms of surgical efficacy and complication control. The patients in our study did not develop nerve injuries such as to the superior laryngeal nerve and recurrent laryngeal nerve as well as other particular complications, which was different from related reports in foreign countries. In our study, the range of microwave ablation was determined by preoperative contrast-enhanced ultrasound. The action time of each ablation point was reduced by multi-point mobile ablation, layer by layer during the operation. Furthermore, additional heat loss was well controlled so that the ablation range was limited to the nodules, and the maximum tumor destruction was achieved with less energy. Therefore, the complications caused by extranodular injury were well controlled.

However, there are some deficiencies in this study. First of all, the lack of a control group in this study drew conclusions through the comparison with other treatments in previous related research may lead to a certain bias. Secondly, this study was a single-center study with a limited sample size. Thirdly, the follow-up time of this study was short. Therefore, a larger sample size and multicenter studies with comparative analysis of multiple treatment options and long-term follow-up are needed to confirm the reliability of this study.

The combination of RFA and lauromacrogol foam sclerotherapy is more effective in the treatment of mixed thyroid nodules, which can reduce the injury, speed up the recovery, and reduce the incidence of complications effectively, achieving good clinical results. The operation provides a new idea for the treatment of mixed nodules and is worthy of clinical application.

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Disclosure of conflict of interest

None.

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