RESEARCH

The influence of nodule size on clinical efficacy of ethanol ablation and microwave ablation on cystic or predominantly cystic thyroid nodules

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Abstract

Objective: To compare the efficacy and safety of ethanol ablation (EA) and microwave ablation (MWA) in the treatment of cystic or predominantly cystic thyroid nodules.

Methods: Patients with cystic or predominantly cystic thyroid nodules intervened with EA or MWA were retrospectively enrolled and divided into EA group (n = 30) and MWA group (n = 31). The volume and volume reduction rate (VRR) of thyroid nodules before ablation, and at 3 and 12 months after ablation were compared between the two groups. The effective rate (ER) and incidence of adverse events in both groups were recorded.

Results: The median VRR and ER at 3 months after ablation were significantly higher in EA group than in MWA group (81.30% vs 75.76%, P = 0.011; 76.67% (23/30) vs 51.61% (16/31), P = 0.040), while no significant difference was detected at 12 months (93.39% vs 88.78%, P = 0.141; 86.67% (26/30) vs 87.10% (27/31), P = 0.960). The median VRR of small nodules in EA group was significantly higher than that in MWA group (81.30% vs 71.18%, P = 0.006; 93.40% vs 83.14%, P = 0.032). There was no significant difference of median VRR in medium nodules at final follow-up between MWA and EA group (93.01% vs 89.68%, P = 0.482). Serious adverse events were not reported in both groups.

Conclusion: EA and MWA are both effective and safe in the treatment of cystic or predominantly cystic thyroid nodules. EA is more cost-effective and effective than MWA for small nodules, but it requires more cycles of treatment and may pose a higher risk of postoperative pain compared with MWA.

Key Words
- ethanol ablation
- microwave ablation
- cystic
- thyroid nodules

Introduction

The incidence of thyroid nodules is increasing annually. Surgery is a preferred management for thyroid nodules, although it has limitations like longer surgical incision, permanent postoperative scars, risk of complications, and long-term postoperative medication. At present, ultrasound-guided minimally invasive treatment for thyroid nodules is becoming popular. Ablation is a typical minimally invasive, non-surgical treatment, which is of great clinical significance in the adjuvant therapy for thyroid nodules.

Ethanol ablation (EA), which can destroy cysts and nodular lesions in multiple organs and tissues, has been
applied to treat thyroid nodules for more than 30 years. Under the guidance of ultrasound, a fine needle is inserted into the thyroid nodule to inject alcohol. Our previous study has shown the acceptable efficacy of EA in treating cystic thyroid nodules (1). A recent meta-analysis showed that EA could significantly reduce the volume of benign cystic thyroid nodules, and the effect was stable over time (2). Based on abundant clinical evidence, EA has been recommended as the first-line treatment for cystic and predominantly cystic thyroid nodules by the 2020 European Thyroid Association Clinical Practice Guideline (3). The efficacy of thermal ablation techniques in the treatment of benign thyroid nodules has been confirmed, mainly including laser ablation, radio frequency ablation, microwave ablation (MWA), and high-intensity focused ultrasound. In 2009, Beak et al. (4) reported that the ablation of large thyroid nodules was performed by moving-shot technique, and the nodules were significantly reduced in volume after surgery. Consistently, our previous study has validated that MWA safely and effectively decreases the volume of benign nonfunctioning thyroid nodules (5). Therefore, MWA has been regarded as an effective treatment for benign thyroid nodules (6).

Though both EA and MWA are effective in the treatment of cystic thyroid nodules, their efficacy has rarely been directly compared. This retrospective study aims to compare the efficacy, safety, and medical cost between EA and MWA in the treatment of cystic or predominantly cystic thyroid nodules.

Methods and materials

Study design and patients

The study was reviewed and approved by the ethics committee of the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine. From January 2013 to April 2020, a total of 621 patients with 685 thyroid nodules were treated in our hospital with EA or MWA. Patients who met the following inclusion criteria were finally included in this retrospective study: (i) benign thyroid nodules with the cystic (CYS, cystic component ≥ 75%) or predominantly cystic component (M-CYS, 50% < cystic component < 75%) examined by ultrasonography; (ii) thyroid nodules with Bethesda category II classified by the Bethesda system for reporting thyroid cytology based on ultrasound and cytological findings (7); (iii) patients with clinical symptoms and signs of local compression, hoarseness, and cosmetic concern; (iv) no history of radiotherapy, surgery for neck cancers, malignancies, and metastatic lymph nodes; and (v) patients requested for interventional treatment after informed consent or refused to surgery.

Totally, we followed 76 patients, 10 patients were followed up for less than 1 year, 5 patients had data missing, and 61 patients with 62 nodules were finally included. They were divided into EA group (31 patients with 31 nodules) and MWA group (30 patients with 31 nodules). Using the criteria employed in previous studies (8, 9), patients were divided into two groups based on thyroid volume at baseline. Patients with small nodules made up group A (nodule volume < 12 mL), and those with medium nodules made up group B (nodule volume ≥ 12 mL). Baseline characteristics, and the volume and ultrasound characteristics of thyroid nodules before ablation, and at 3 and 12 months after ablation were recorded for analyses. Ultrasound images of all thyroid nodules were retrospectively reviewed and scored using the 2020 Thyroid Imaging Reporting and Data System of Chinese Medical Association (C-TIRADS) (10).

Ablation procedure

During the procedure, patients remained in a supine position with mild neck extension. After disinfection using 0.2% iodine and paving sterile sheets, ultrasound-guided local infiltration anesthesia using 1% lidocaine was performed on the lesion site. Normal saline was continuously injected into the space between the thyroid capsule and trachea, esophagus, recurrent laryngeal nerve, and parathyroid gland to safely separate the nearby structures of the neck. Under the guidance of ultrasound, cystic fluid was aspirated as much as possible before MWA. Then, an MWA needle (KY-2000 microwave generator, Kangyou Applied Research Institute, Nanjing, China) was inserted and punctured into the thyroid nodule along the ablation path. Using the moving-shot technique, multipoint ablation was performed to fully cover the whole thyroid nodule. In the EA group, after cystic fluid was aspirated, 98% alcohol was injected into the thyroid nodule under the guidance of ultrasound for three times of irrigation. Absolute alcohol corresponding to 50% of the volume of the residual thyroid nodule was injected into the cystic space for retention, which was injected into the solid space corresponding to 100% of the total volume of the solid component. EA was completed until ultrasound-confirmed hyperechogenicity in the injected solid component. Pressurized ice compress was postoperatively performed for 30 min.
**Outcome measurement**

The volume (V) and volume reduction rate (VRR) of thyroid nodules before ablation, and at 3 and 12 months after ablation, and effective rate (ER) were calculated using the following equations: 

\[ V (\text{mL}) = \pi \frac{abc}{6}, \]

where a, b, and c were the three maximum perpendicular diameters shown on the ultrasound image; 

\[ \text{VRR} \% = \left( \frac{\text{preoperative} \ V - \text{postoperative} \ V}{\text{preoperative} \ V} \right) \times 100\%; \]

\[ \text{ER} \% = \frac{\text{number of successfully treated cases (with VRR} \geq 75\%)}{\text{total case number}} \times 100\% \ (\text{II}). \]

**Statistical analysis**

Statistical analysis was performed using SPSS 24.0. Normally distributed measurement data were expressed as mean ± standard deviation (\( \bar{X} \pm \text{s.d.} \)), and differences between and within two groups were detected by the independent sample t test and paired sample t test, respectively. Measurement data that did not conform to the normality were expressed as M (P25–P75), and compared by the Wilcoxon rank sum test. Logistic regression and linear regression analysis were performed to identify potential influencing factors for the efficacy of ablation. \( P < 0.05 \) was considered as statistically significant.

**Results**

**Baseline characteristics**

Sixty-one patients with cystic or predominantly cystic thyroid nodules were recruited, involving 31 patients in EA group and 30 in MWA group. One patient in the EA group had nodule regrowth at 6 months after ablation and was then transferred to MWA. Sixty patients with 61 nodules were finally included (Fig. 1). There were 3 male and 27 female patients in EA group, and 1 male and 29 female patients in MWA group. The maximum diameter of the thyroid nodule (2.96 ± 0.78 cm vs 3.75 ± 0.97 cm, \( P < 0.05 \)), mean volume of thyroid nodule (4.92 (2.93–10.19) mL vs 8.33 (4.95–14.80) mL, \( P < 0.05 \)), and medical cost (1117.73 ± 55.22 USD vs 2457.29 ± 278.08 USD, \( P < 0.001 \)) were significantly lower in EA group than in MWA group, while EA group required more treatment cycles (2.5 (1.0–3.3) times vs 1 (1.0–1.0) time, \( P < 0.001 \)). Between the two groups, there was a significant difference in the C-TIRADS classification (\( P = 0.010 \)) (Table 1).

**Overall therapeutic efficacy**

The median Vs before ablation, and at 3 and 12 months after ablation in EA group were 4.92, 0.86, and 0.39 mL,
and 8.33, 1.99, and 0.98 mL in MWA group, respectively. Postoperative V was significantly reduced compared with that at baseline in both groups (all \( P < 0.001 \)) (Fig. 2 and Table 2). The median VRR and ER at 3 months after ablation were significantly higher in EA group than in MWA group (81.30% vs 71.18%, \( P = 0.006 \); 93.40% vs 83.14%, \( P = 0.032 \)), while no significant difference was detected between the two treatment modalities during follow-up in group B (82.71% vs 79.71%, \( P = 0.688 \); 89.68% vs 93.01%, \( P = 0.482 \)). After MWA, the median VRR was higher in group B than in group A, but the difference was only statistically significant at 12 months (93.01% vs 83.14%, \( P = 0.015 \)). Moreover, after EA, no significant difference was observed in VRR between group A and group B during the follow-up (Table 4).

### Therapeutic efficacy in treating small and medium thyroid nodules

In group A, the median VRRs at 3 and 12 months after ablation were significantly higher in EA group than in MWA group (81.30% vs 75.76%, \( P = 0.011 \); 76.67% vs 51.61%, \( P = 0.040 \)), while no significant difference was detected between the two treatment modalities during follow-up in group B (82.71% vs 79.71%, \( P = 0.688 \); 89.68% vs 93.01%, \( P = 0.482 \)). After MWA, the median VRR was higher in group B than in group A, but the difference was only statistically significant at 12 months (93.01% vs 83.14%, \( P = 0.015 \)). Moreover, after EA, no significant difference was observed in VRR between group A and group B during the follow-up (Table 4).

### Therapeutic efficacy in treating cystic and predominant cystic thyroid nodules

Thyroid nodules included in this study were further divided into CYS and M-CYS ones based on the cystic component. There were 18 (60.00%) and 9 (29.03%) CYS

### Table 1 Baseline characteristics of patients with cystic or predominant cystic thyroid nodules (\( n = 61 \)).

| Characteristic          | EA group | MWA group | \( P \) value |
|-------------------------|----------|-----------|--------------|
| Patients/nodules (n)    | 30/30    | 30/31     |              |
| Male/female (n)         | 3/27     | 1/29      |              |
| Cystic component        |          |           |              |
| \( \geq 75\% \) (CYS)   | 18 (60%) | 9 (29.03%)|              |
| 50–75\% (M-CYS)         | 12 (40%) | 22 (70.97%)|              |
| Age (years)             | 45.87 ± 12.95 | 40.10 ± 15.18 | 0.131       |
| Maximum diameter (cm)   | 2.96 ± 0.78 | 3.75 ± 0.97   | 0.001       |
| Volume (mL)             | 4.92 (2.93–10.19) | 8.33 (4.95–14.80) | 0.020       |
| C-TIRADS classification  | 2 (2–2)  | 2 (2–3)   | 0.011       |
| Medical cost (USD)      | 111.73 ± 55.22 | 2457.29 ± 278.08 | 0.000       |

CYS, cystic; C-TIRADS, the Thyroid Imaging Reporting and Data System of Chinese Medical Association; EA, ethanol ablation; MWA, microwave ablation; M-CYS, predominantly cystic.

The age, V, and VRR of thyroid nodules were introduced into the logistic and linear regression analysis to identify potential factors influencing the efficacy of ablation. Age was significantly correlated with VRR at 12 months after ablation (\( t = 2.09, P = 0.041 \)) (Table 3).

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**Figure 2**

Ultrasound results of thyroid nodules before and after ablation. (A) A 33-year-old female patient with the volume of thyroid nodule before EA of 3.59 mL, which was reduced to 0.37 mL (VRR = 89.81%) and 0.07 mL (98.12%) at 3 and 12 months, respectively, after ablation. (B) A 45-year-old male patient with the volume of thyroid nodule before MWA of 11.39 mL, which was reduced to 2.07 mL (VRR = 81.84%) and 0.66 mL (94.22%) at 3 months and 12 months, respectively, after ablation. EA, ethanol ablation; MWA, microwave ablation.
thyroid nodules in EA and MWA groups, and 12 (40.00%) and 22 (70.97%) M-CYS thyroid nodules in EA and MWA groups, respectively. The median VRR of CYS thyroid nodules during the follow-up period was higher than that of M-CYS ones. There was no statistically significant difference in VRR between the two treatment modalities during follow-up based on cystic component proportions (all \(P > 0.05\)) (Table 5).

**Adverse events**

No serious adverse events were reported during the ablation procedure and follow-up period. The incidence of mild injection site pain and/or postoperative tenderness was slightly lower in MWA group than that in EA group (8 (26.67%) vs 6 (19.35%), \(P = 0.497\)), both relieved within 1 week without the use of analgesics. All patients were tolerant to EA or MWA, and hematoma, hoarseness, facial paralysis, and local infection were not reported.

**Discussion**

Thyroid nodules are common, with an overall prevalence of 36.9% in China (12). In recent years, the detection rate of thyroid nodules has risen up to 68% with the widespread application of ultrasonography (13). Only 5–10% of thyroid nodules are malignant, and the majority are benign that need no clinical treatment (14, 15). Currently, the efficacy and safety of EA and thermal ablation on cystic or predominantly cystic thyroid nodules have been validated (1, 2, 3, 16, 17).

EA causes a sterile inflammatory response by directly inducing cell dehydration, protein coagulation, denaturation, and necrosis using alcohol. It inhibits the secretory function of epithelial cells and blocks tumor blood supply, thus leading to the adhesion and closure of the nodular cavity and shrinkage of tumor. However, the recurrence rate remains high after EA for predominantly cystic nodules, and the efficacy of multi-injection of alcohol is controversial (18). Generally speaking, the number of alcohol injection cycles is determined by the initial volume of the tumor, treatment response, and follow-up findings, and most cases require two to three times of injection. Nevertheless, the risk of complication increases with the treatment cycle. In the present study, the median treatment cycle in EA group was 2.5 (1.0–3.3) times, and eight patients complained of mild pain, with an incidence (26.67%) slightly higher than that in MWA group. The high incidence of pain during ablation procedure and follow-up period may be attributed to the difficulty in controlling the diffusion of alcohol solution to the thyroid nodule and the surrounding tissue space, leading to the hemorrhage of normal thyroid glands and surrounding tissues caused by stimulation, destruction, and even necrosis. The VRR of cystic thyroid nodules after EA was significantly higher than that of predominantly

### Table 2
EA and MWA outcomes after ablation in patients with cystic or predominant cystic thyroid nodules (\(n = 61\)).

|                          | EA group (\(n = 30\)) |       | MWA group (\(n = 31\)) |       |
|--------------------------|-----------------------|-------|------------------------|-------|
|                          | Baseline              | 3 months | 12 months               |
| V (mL)                   | 4.92 (2.93–10.19)     | 0.86 (0.44–1.65)\(^a\) | 0.39 (0.08–0.88)\(^b\) |
| VRR (%)                  | -                     | 81.30 (74.46–90.96) | 93.39 (81.28–97.67)\(^b\) |

\(^a\) \(P < 0.001\) vs baseline; \(^b\) \(P < 0.001\) vs 3 months.

EA, ethanol ablation; MWA, microwave ablation; V, volume; VRR, volume reduction rate.

### Table 3
Influencing factors for VRR and ER.

|                      | VRR at 12 months | ER |                      |
|----------------------|------------------|----|----------------------|
|                      | Linear regression | Logistic regression |
|                      | \(t\) \(P\) value | OR (95% CI) \(P\) value |
| Age                  | 2.09 0.041       | 1.02 (0.97–1.08) 0.464 |
| Volume               | 1.44 0.155       | 1.17 (0.86–1.58) 0.319 |
| Max diameter         | -0.64 0.522      | 0.70 (0.14–3.48) 0.664 |

ER, effective rate; OR, odds ratio; VRR, volume reduction rate.

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cystic ones. Our previous study has reported higher VRR of cystic thyroid adenomas after EA than that of solid ones (1). It is suggested that the therapeutic efficacy of EA is less influenced by the cystic component of nodules.

The frequency of microwave radiation ranges 900–2450 MHz. The interaction between radiation-induced oscillating charges and water molecules causes vibration, and the violent friction between the molecules based on the frequency of microwave radiation in turn produces heat. Electromagnetic microwaves produce friction and heat through water molecules in the surrounding tissues, thus inducing cell death via coagulative necrosis (19). Due to the controllable power, ablation time, and ablation range, electromagnetic microwaves remarkably reduce the stimulation and damage to the normal thyroid and surrounding tissues. Our previous studies have shown the acceptable efficacy and safety of MWA on benign thyroid nodules, papillary thyroid microcarcinoma, and primary hyperparathyroidism (5, 20, 21). The median VRR of benign thyroid nodules at 6 and 12 months of MWA reaches 75.9 and 86.67%, respectively (5). However, the efficacy of MWA on cystic or predominantly cystic thyroid nodules remains unclear. In the present study, the median VRR at 3 and 12 months of MWA was 75.76 and 88.78%, respectively. Luo et al. (17) conducted a 3-year follow-up in patients with thyroid nodules and found that the VRR of solid nodules at 1, 3, and 6 months postoperatively is significantly lower than that of cystic and predominantly cystic ones, while no significant correlation is identified between cystic component and VRR at 12, 24, and 36 months postoperatively. It is indicated that the component of thyroid nodules may not influence the long-term efficacy of MWA.

Our study proved that both EA and MWA could significantly shrink cystic or predominantly cystic thyroid nodules. VRR and ER were higher in EA group during the follow-up period than in MWA group, although significant difference was only detected at 3 months after ablation. This difference may be attributed to the significantly smaller volume of thyroid nodules at baseline in EA group, compared with that of MWA group. Previous evidence has supported the negative correlation between the therapeutic efficacy of ablation and initial volume of nodules (22, 23). Therefore, we further evaluated the effect of nodule volume on the efficacy of EA and MWA. We found that the median VRR of small nodules in EA group was significantly higher than that in MWA group. Meanwhile, the median VRR of medium nodules at final follow-up was higher in MWA group, but there was no statistical difference. These suggest that EA is suitable for small-volume cystic or predominantly cystic thyroid nodules, and MWA for larger-volume nodules.

Currently, the comparison between the clinical efficacy of EA and MWA has been rarely reported. Liu et al. (24) reported the similar efficacy of EA and MWA on simple thyroid cysts, although the incidence of intraoperative pain was lower in MWA group than in EA group. Zhou et al. (25) demonstrated the superb efficacy of MWA with less damage in treating benign solid-cystic thyroid nodules, compared with EA. The combination of EA and MWA has been reported to significantly shorten the procedure time and reduce the recurrence in patients

| Table 4 | VRR of small and medium thyroid nodules. |
|---|---|
| **VRR at 3 months** | **VRR at 12 months** |
| | Group A | Group B | Group A | Group B |
| EA | 81.30 (73.30–91.26) | 82.71 (75.35–90.61) | 93.40 (78.42–98.09) | 93.01 (89.28–95.41)* |
| MWA | 71.18 (54.52–79.20) | 79.71 (65.31–89.33) | 83.14 (76.64–93.25) | 89.68 (81.28–95.41)* |
| P value | 0.006 | 0.688 | 0.032 | 0.482 |

*P < 0.05 vs group A.

EA, ethanol ablation; Group A, patients with small nodules (nodule volume < 12 mL); Group B, patients with medium nodules (nodule volume ≥ 12 mL); MWA, microwave ablation; VRR, volume reduction rate.

| Table 5 | VRR of cystic and predominantly cystic thyroid nodules. |
|---|---|
| **VRR at 3 months** | **VRR at 12 months** |
| | CYS | M-CYS | CYS | M-CYS |
| EA | 85.17 (78.60–92.91) | 76.98 (56.69–88.92) | 94.80 (88.22–98.03) | 86.14 (75.04–93.53)* |
| MWA | 79.71 (69.91–90.94) | 71.71 (46.28–79.68)* | 93.21 (90.78–97.08) | 83.98 (77.72–93.23)* |
| P value | 0.237 | 0.207 | 0.504 | 0.914 |

*P = 0.045 vs CYS group; **P = 0.038 vs CYS group; ***P = 0.030 vs CYS group.

CYS, cystic (cystic component ≥ 75%); EA, ethanol ablation; MWA, microwave ablation; M-CYS, predominantly cystic (50% < cystic component < 75%); VRR, volume reduction rate.
with predominantly cystic thyroid nodules (26). In the present study, the median VRR of CYS thyroid nodules during the follow-up period was higher than that of M-CYS ones. The results showed that a greater cystic component proportion can trigger a stronger response to ablation. Moreover, there was no statistically significant difference in VRR between the two treatment modalities during follow-up based on cystic component proportions.

This study was limited by the small sample size, short follow-up period, and differences in baseline characteristics. We did not perform propensity score matching to eliminate potential interventions in control group. Our findings should be further validated in randomized clinical trials with a large sample size, and the therapeutic efficacy of EA combined with MWA in treating thyroid nodules should be investigated in the future.

Taken together, both EA and MWA are effective and safe in the treatment of cystic or predominantly cystic thyroid nodules. EA is more cost-effective and effective than MWA for small nodules, but it requires more cycles of treatment and may pose a higher risk of postoperative pain than MWA.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Ethical approval and consent to participate
The studies involving human participants were conducted according to the ethical guidelines of the Helsinki Declaration and approved by the ethics committee of the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine. Verbal informed consent was obtained from all patients by telephone.

Availability of data and materials
Datasets generated in this study are available on request to the corresponding author.

Author contribution statement
Ya Zhang and Shuhang Xu developed the research questionnaire and prepared the protocol for this study. Ya Zhang and Yuling Liu were responsible for data collection and analysis. Guofang Chen, Xin Hu and Pingping Xiang participated in the diagnosis. Shuhang Xu and Xiaojiu Chu performed microwave ablation and ethanol ablation. Yueting Zhao and Xue Han were responsible for the perioperative management. Shuhang Xu, Xiaojiu Chu and Chao Liu were responsible for data analyses. Ya Zhang and Yuling Liu drafted the manuscript. Shuhang Xu and Chao Liu revised the draft critically for important intellectual content. All authors agreed to take responsibility for the integrity of the data and the accuracy of data analysis, and approved the final version of the manuscript.

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