Comparison of microwave alone and combined with ethanol ablation for different types of benign cystic solid thyroid nodules

Jun Wu (✉ wujun201866@163.com)  
First Affiliated Hospital of Anhui Medical University  https://orcid.org/0000-0002-5977-6837

Chaoxue Zhang  
First Affiliated Hospital of Anhui Medical University

Fan Jiang  
Second Affiliated Hospital of Anhui Medical University

XiaoFeng Lan  
Second Affiliated Hospital of Anhui Medical University

Xiang Xie  
Second Affiliated Hospital of Anhui Medical University

Research Article

Keywords: Cystic solid nodules, microwave ablation, ethanol ablation, the inactivation rate, volume reduction rate

Posted Date: April 11th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2672797/v1

License: ☒  This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Abstract

Objective

To evaluate the efficacy and safety of microwave ablation (MWA) plus ethanol ablation (EA) for different types of benign cystic solid thyroid nodules.

Methods

A total of 81 patients with 81 benign cystic solid thyroid nodules were enrolled into the study; 39 were divided to the MWA group and 42 to the combined group (MWA combined with EA). Nodule inactivation rate, volume reduction rate (VRR) and surgical complications of all patients were analyzed before and after treatment.

Results

The mean inactivation rate were 86.49 ± 6.68% and 90.09 ± 5.79% in the microwave and combined groups respectively, and the inactivation rate of nodule decreased as the nodule volume increased. For nodules ≥ 15 ml in volume, the mean inactivation rate of the combined group was higher than that of the microwave group (all \( P < 0.05 \)). The mean VRR at 12 months postoperatively was 89.58 ± 4.32% in the microwave group and 92.92 ± 3.49% in the combined group, showing statistical significantly different between both arms \( (P = 0.001) \). The combined group decreased in volume more significantly than the microwave group for nodules with 20%-50% or 50%-80% cystic proportions or > 15 ml in volume (all \( P < 0.05 \)). The complication rate was 23.08% and 2.38% respectively.

Conclusion

MWA combined with EA is more effective than MWA for treating cystic solid thyroid nodules. MWA combined with EA may be the first approach for nodules with > 20% cystic proportions or volume > 15 ml.

Introduction

Thyroid nodules have developed into a common disease in China and worldwide, with the total detection rate as high as 68% [1]. Ultrasound reveals that between 15% and 25% of isolated nodules are cystic solid or cystic [2–4]. Most cystic or cystic solid nodules are benign, asymptomatic and treatment is not necessary [5]. Nevertheless, The American Thyroid Association (ATA) suggested that cystic solid thyroid nodules require regular observation and specific treatments because of the enlarged size of the nodules causing neck discomfort, patient concerns or signs of malignancy [6, 7]. The initial treatment was the simple aspiration of the cystic components, which not only reduced the volume of the nodule, but also allowed for qualitative diagnosis [8]. However, this method has an 80% recurrence rate [9]. Ethanol ablation has been shown to have good results in cases of recurrence after aspiration [10, 11].
Although ethanol ablation (EA) is effective in the treatment of cystic or cystic solid nodules, 5%-25% of patients do not respond well to EA [2, 3]. In these poorly treated cases, the efficacy of repeat EA is also significantly reduced [12, 13]. EA has been shown to be the best first-line technique for benign cystic thyroid nodules [11, 14]; but EA as the first technique for cystic solid thyroid nodules is controversial as the repeat rate of EA is > 50% in those nodules with < 80% cystic content [13, 15, 16]. Recently, several studies have shown that radiofrequency ablation or microwave ablation (MWA) could be applied to treating cystic solid thyroid nodules with good results and few complications [7]. Nevertheless, intracapsular bleeding often occurs during radiofrequency or MWA, which affects the outcome of the treatment and leads to treatment failure. The main cause is the puncture of blood vessels in the bursal wall by the puncture needle, and the cystic cavity bleeds from the rupture of the blood vessels in the cystic wall due to the reduced pressure in the cyst after aspiration [17]. Intraoperative bleeding enlarges the nodule volume and the fluid dissipation effect reduces the efficacy of thermal ablation [18]. Other studies have reported that EA can stop bleeding and MWA combined with EA for cystic solid thyroid nodules is a safe and effective method [19]. Despite these evidences, no research has assessed the efficacy of MWA combined with EA for different types of benign cystic solid thyroid nodules.

This study therefore aims to compare the efficacy and safety of microwave alone and combined with EA for different types of benign cystic solid thyroid nodules. Eighty-one patients who met the criteria were included and divided to the MWA and the combined groups. Clinical results were analyzed for all the patients.

**Methods And Materials**

**Study design**

This retrospective observational research was permitted by the Ethics Committee of the Second Hospital of Anhui Medical University (YX2023-004). Written informed agreement was obtained from each participant before treatment. All relevant clinical and therapeutic informations were prospectively documented.

**Patients**

A total of 81 patients with 81 benign cystic solid thyroid nodules received ablation in the Second Affiliated Hospital of Anhui Medical University from May 2019 to October 2021 were enrolled. Patients were then treated with MWA alone or MWA combined with EA (Fig. 1). The inclusion criteria for patients were as follows: (1) ultrasonography showed a single cystic solid nodule with clear border, regular morphology and no signs of malignancy such as burr, calcification or abnormal aspect ratio; (2) thyroid nodule volume > 5 ml, and the cystic components of the nodule was less than 80%; (3) preoperative fine needle aspiration biopsy of both the cystic and solid parts of the nodule was performed and the diagnosis was benign; (4) those who have symptoms of pressure, cosmetic problems or psychological burden and voluntarily requested treatment.
Preoperative evaluation and equipment

The three diameters of the nodules (maximum diameter, a and two vertical diameters, b and c) were performed by ultrasound before surgery. The nodule volume was computed by applying the formula: \( V = \pi \frac{a*b*c}{6} \). Meanwhile, the three subgroups were subdivided by nodules volume (< 15 ml, 15 ~ 30 ml, > 30 ml) or cystic percentage (< 20%, 20 ~ 50%, 50 ~ 80%) before treatment.

ACUSON S2000 (Siemens, Germany) with probe L6 was used for thyroid ultrasound. SonoVue (Bracco, Italy), an ultrasound contrast agent, was applied to contrast-enhanced ultrasound (CEUS). An ECO-100A13 microwave ablation instrument (ECO, China) with a 16-guage single use microwave ablation needle was performed for treatment. Output power was adjusted at 35W during the procedure.

Ablation procedure

The patient was placed in the supine position with full exposure of the neck. An indwelling needle was also placed in the patient’s anterior elbow vein to open venous access. Colour Doppler ultrasound and CEUS were used to assess the location, size, morphology, blood supply and anatomical relationships of the surrounding vital structures of the nodule before surgery, and to determine the puncture point and route of access. Routine disinfection, towel laying and subcutaneous local anesthesia with 2% lidocaine were performed. About 15 ml of 0.9% saline was injected to separate the thyroid from the carotid space, the thyroid from the tracheal space, the thyroid from the oesophagus and the posterior thyroid space (the area of the recurrent laryngeal nerve travels) to form a “fluid barrier” to protect the vital structures from thermal injury. A 16-guage puncture needle was then inserted into the cystic portion of the nodule under ultrasound guidance and the cystic fluid was withdrawn. If the cystic fluid was too thick to be aspirated, the cystic cavity was repeatedly flushed with saline until the fluid could be aspirated. Afterward the cystic cavity was then flushed with 95% anhydrous ethanol in the combined group (flushing volume was 1/3 of the amount of cystic fluid withdrawn). The cystic cavity was flushed 3 ~ 5 times until the fluid became clear. Finally microwave ablation was performed on the solid portion. The whole process was shown in Fig. 2. In the MWA group, the microwave needle was inserted into the nodule after the cystic uid had been aspirated and the nodule was ablated on multiple points and surfaces until the nodule was covered by strong echogenicity. CEUS immediately after ablation was performed in two groups.

Follow-up

The nodule inactivation rate was assessed by CEUS immediately after surgery (inactivation rate = [postoperative volume without perfusion] / preoperative volume of nodal perfusion×100%). Volume reduction rate (VRR) was followed up at months 3, 6, 9 and 12 postoperatively. VRR =((baseline volume - postoperative volume)×100%) / baseline volume, VRR (12 months after surgery) > 50% was considered successful.

Statistical Analysis
SPSS software, version 22.0, was employed for the statistical evaluations. Quantitative parameters were presented as mean ± standard deviation (SD), and qualitative parameters were presented as percentage or number. Quantitative data were compared by means of the t-test. Qualitative data were analysed with the Chi-square test or Fisher's exact test. Differences were considered statistically significant at $P < 0.05$.

**Result**

**Patient characteristics**

The clinical data of the participants enrolled in two groups are shown in Table 1. There was not significant statistical difference between both groups with regard to age, gender, initial volume, compression symptom, or cosmetic problem (all $P > 0.05$). Of note, there was no statistically significant difference in nodule volume or cystic proportions between the corresponding subgroups in two groups ($P > 0.05$).

**Table 1** Comparison of the parameters of the patients in both groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Microwave group</th>
<th>Combined group</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>39</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>47.3 ± 7.5</td>
<td>46.0 ± 8.3</td>
<td>0.46</td>
</tr>
<tr>
<td>Male/female</td>
<td>13/26</td>
<td>16/26</td>
<td>0.82</td>
</tr>
<tr>
<td>Baseline volume (ml)</td>
<td>13.77 ± 8.96</td>
<td>14.56 ± 7.66</td>
<td>0.67</td>
</tr>
<tr>
<td>Pressure symptom</td>
<td>7</td>
<td>5</td>
<td>0.54</td>
</tr>
<tr>
<td>Cosmetic problem</td>
<td>6</td>
<td>4</td>
<td>0.51</td>
</tr>
</tbody>
</table>

**Efficacy evaluation**

Comparison of inactivation rate of thyroid nodules of different volumes by contrast-enhanced ultrasound immediately after ablation were analyzed in Fig. 3a. The mean inactivation rate were 86.49 ± 6.68% and 90.09 ± 5.79% in the microwave and combined groups respectively, and the inactivation rate decreased with increasing nodule volume in each group. For patients with nodule volume of less than 15 ml, the mean inactivation rate was 91.53 ± 4.13% in the microwave group and 93.28 ± 3.56% in the combined group, for a mean difference of -1.75% (95% confidence interval, -3.72 to -0.22) ($P = 0.08$). For patients having nodule volume between 15 and 30 ml, the mean inactivation rate was 89.23 ± 3.41% in the microwave group and 91.29 ± 3.67% in the combined group, for a mean difference of -2.07% (95% CI, -3.91 to -0.22) ($P = 0.03$). For patients having nodule volume of more than 30 ml, the mean inactivation rate of the microwave group was 78.71 ± 3.37%, and that of the combined group was 85.68 ± 3.46%, for a mean difference of -6.98% (95% CI, -8.25 to -5.20) ($P < 0.001$).
The mean VRR of the two groups are showed in Fig. 3b. The VRR in the microwave group at 3, 6, 9 and 12 months after surgery were 55.24 ± 6.35%, 76.80 ± 7.54%, 87.04 ± 5.58% and 89.58 ± 4.32% respectively. The VRR of the combined group at 3, 6, 9 and 12 months after treatment were 61.39 ± 6.25%, 81.95 ± 2.83%, 91.71 ± 3.58% and 92.92 ± 3.49% respectively. At the four post-operative follow-up visits, the differences in nodule volume reduction between the two groups were statistically significant, with mean changes of -6.15% (95% CI, -9.41 to -2.90) (P< 0.01), -5.15% (95% CI, -8.38 to -1.92) (P< 0.001), -4.67% (95% CI, -7.22 to -2.11) (P< 0.01), and -3.34% (95% CI, -5.33 to -1.35) (P< 0.01) respectively. In addition, there were statistically significantly differences in VRR between groups at 3 months versus 6 months and at 6 months versus 9 months postoperatively in each group (all P< 0.001), and not clinically significantly different in VRR between groups at 9 months and 12 months after surgery (all P> 0.05).

By 12-month post-operative follow-up, the difference in VRR between the microwave group and the combined group was not statistically significant for patients with less than 20% of nodules cystic (91.17 ± 4.04% vs 91.85 ± 3.49%; P= 0.478). However, the combined group decreased in volume more significantly than the microwave group for patients with 20%~50% and 50%~80% nodular cystic proportions at the 12 month follow-up (VRR, 93.28 ± 3.30% vs 89.69 ± 3.96%, P< .01; 91.45 ± 3.35% vs 86.45 ± 3.25%, P< 0.01) (Fig. 3c). The results also showed that at 12 months post-ablation, the mean VRR of thyroid nodules decreased in each group as the nodule volume increased in each group (all P< 0.05); and the nodal VRR in the microwave group was less than that in the combined group when the nodule volume was 15 ~ 30 ml and greater than 30 ml (91.58 ± 4.30% vs 93.80 ± 3.43%, P= 0.028; 82.70 ± 4.54% vs 86.38 ± 5.18%, P= 0.006) (Fig. 3d).

**Safety evaluation**

In the microwave group, 12.8% (5/39) of nodules had intracystic hemorrhage during surgery, 7.69% (3/39) of nodules had hoarseness, and 2.56% (1/39) of nodules had postoperative fever. However, only 2.38% (1/42) of nodules in the combined group developed hoarseness, with no other complications. In comparison with the microwave group, the combined group reduced the occurrence of surgical complications, with a statistically significant difference (P= 0.013). All patients had no serious complications. The patients with surgical complications reduced to zero at the 3-month post-operative follow-up (Table 2).
Discussion

In this study, we retrospectively analyzed the efficacy and safety of microwave alone and combined with EA for different types of benign cystic solid thyroid nodules. We found that MWA combined with EA significantly improved nodule inactivation rate and reduced the nodule volume in the treatment of benign cystic solid thyroid nodules. All patients were followed up with a VRR > 50% at 12 months after surgery in both groups. In addition, no serious complications occurred intraoperatively or at follow-up.

Enhanced ultrasound result immediately after ablation showed that the inactivation rate of nodule decreased as the nodule volume increased in this study. The reduced inactivation rate may be due to the fact that ablation can not be completed in a single session when the nodule volume is > 15 ml and the irregular shape of the solid portion of the cystic nodule makes it difficult to access the needle during the procedure. The sonogram of ablation portion appears hyperechoic, somewhat obscuring the previous nodal boundary and the extent of ablation. This affects the subsequent ablation. One study has showed that radiofrequency combined with EA was more effective in solid benign thyroid nodules with > 10 ml in volume and improved patient satisfaction [20]. For patients with nodule volume > 15 ml, the inactivation rate was higher in the combined group than in the microwave group in the present study, probably because intracapsular hemorrhage often occurs during the procedure of larger nodules. In the combined group, EA has an intracapsular hemostatic effect after cyst fluid aspiration, and nodule volume reduction facilitates the deposition of thermal ablation energy, especially when the nodule volume is > 30 ml. Energy to volume ratio has been shown to be an independent factor in the efficacy of ablation of benign thyroid nodules [21].

This study has confirmed that the VRR of thyroid nodules was higher in the combined group than in the microwave group at the 3, 6 and 9 month postoperative follow-ups. Yoon et al. [22] reported that radiofrequency combined with EA of cystic solid thyroid nodules was an effective and safe technique that reduced the average nodule volume by 17.1 ml to 4.3 ml. Our study also found that the significant
reduction in volume of thyroid nodules was at 3 months after surgery in both groups, which was consistent with other studies [23, 24].

The combined group decreased in volume more significantly than the microwave group for patients with 20%~50% and 50%~80% nodular cystic proportions at the 12 month follow-up. The reason for this result is that ethanol ablation can damage the nodal cyst wall to prevent bleeding, but does not affect the solid component within the nodule well. And the more cystic components there are, the higher VRR of the nodules [25]. For nodules with < 20% cystic components, MWA alone was effective due to the low probability of blood leakage after a small amount of cystic fluid aspiration. Therefore, there was no statistical difference in nodal VRR between the two groups for nodules with < 20% cystic components at 12-month post-operative follow-up. The results of this study also demonstrated that at 12 months post-ablation, the mean VRR of thyroid nodules decreased in each group as the nodule volume increased. The initial nodule volume may influence the efficacy of radiofrequency ablation [26]. Huh et al. [27] reported that additional ablation was required to achieve results for initial nodule volume > 20 mL. Jeong et al. [28] reported that an average of 1.4 treatment sessions were required for thyroid nodules with average of 6.1 ml in volume, and Lim et al. [29] reported that an average of 2.2 treatment sessions were required for thyroid nodules with an average volume of 9.8 ml. All patients in this study completed treatment in one session. For the nodules with >15 ml in volume, the mean inactivation rate of the combined group was above that for the microwave group. Hence, the nodule VRR in the microwave group was less than that in the combined group when the nodule volume was 15 ~ 30 ml and greater than 30 ml.

In the microwave group, five patients had intraoperative bleeding, which was stopped by the use of microwave needles and then continued with treatment; one patient developed a fever of up to 38.5°C, which was relieved by antipyretic treatment. Postoperative hoarseness occurred in three of the five patients with intraoperative bleeding, and one patient in the combined group had hoarseness. It was considered that the pre-existing nodule was large or there was intracapsular haemorrhage in the nodule, close to the recurrent laryngeal nerve. The ablation took a long time and during the procedure the isolation fluid was absorbed at the same time, resulting in insufficient thickness of insulation and causing a slight burn to the recurrent laryngeal nerve. That was treated with hormonal therapy and recovered after 3 months.

However, our study had a few shortcomings. First, the study design was based on a retrospective surgery with large bias or confounding factors. Second, the number of follow-up patients was poor and short. Third, there was no EA alone as the control group. In the future, multi-centre prospective studies will need to be done to confirm our results.

**Conclusions**

In summary, MWA combined with EA is an effective and safe method in the treatment of benign cystic solid thyroid nodules. MWA combined with EA may be the first approach for nodules with >20% cystic components or volume >15 ml (nodules with < 80% cystic content).
Declarations

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest between them.

Authors' contributions J.W and C.X.Z planned the direction of this research. J.W, X.F.L, and X.X collected the data needed for the study. J.W wrote the manuscript. C.X.Z and F.J helped to revise the manuscript.

References


Figures
Figure 1

Flow diagram of the participants enrolled in this research.
Figure 2

Preoperative two-dimensional ultrasound, CDFI and CEUS images of the nodule (with <20% cystic proportions, a-c). Image of EA after aspiration of nodule cyst fluid in combined group (d). Image of solid component MWA after EA of the nodule (e). CEUS image immediately after nodule ablation (f).
Figure 3

Comparison of inactivation rate after ablation of thyroid nodules of different volumes between the two groups (a). Comparison of mean VRR between the two groups at 3, 6, 9 and 12 months after ablation, and comparison of mean VRR between adjacent 3 months within each group (b). Comparison of mean VRR of thyroid nodules with different degrees of cystic fluid between the two groups at 12 months after ablation (c). Comparison of mean VRR of thyroid nodules of different volumes between the two groups at
12 months after ablation, and comparison of mean VRR of thyroid nodules of different volumes within each group (d).