Original Article

The association between volume reduction ratio and time after ultrasound-guided microwave ablation for benign thyroid nodules of different compositions

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Background: Ultrasound-guided microwave ablation (MWA) is effective in the treatment of benign thyroid nodules (BTNs); however, there are large individual differences in the degree of lesion absorption and shrinkage speed. Although the internal components of nodules are important influential factors, few studies have reported temporal changes in the volume reduction ratio (VRR) in BTNs with different compositions. Therefore, this study aimed to explore how the thyroid nodule VRR changes over time and determine when it increases most significantly for BTNs of different compositions after MWA.

Methods: This is a retrospective study. We consecutively collected patients that received MWA for BTNs from July 2020 to June 2021, with 12 months of follow-up, and VRR >50% as effective treatment indicator. A generalized additive model was used to analyze temporal changes in the VRR in BTNs of different compositions, and a log-likelihood ratio test of the segmented regression model was used to determine a potential threshold. We evaluated the consistency of two operators in MWA of BTNs.

Results: In total, 221 treatment-effective nodules (216 patients) were included, in which 21 were predominantly cystic, 61 were predominantly solid, and 139 were solid nodules. A non-linear relationship was detected between VRR and time. In predominantly cystic nodules, the VRR increased by 36% per month until 2.0 months and by 1.4% per month after 2.0 months. In predominantly solid nodules, the VRR increased by 30.6% per month until 2.3 months and by 0.7% per month after 2.3 months. In solid nodules, the VRR increased by 17.4% per month until 4.3 months and by 0.3% per month after 4.3 months. Intraclass correlation coefficient (ICC) was 0.839 (95% confidence interval: 0.773, 0.887), indicating good consistency between the two operators.

Conclusions: The VRR after ultrasound-guided MWA for different components of BTNs was non-linearly related with follow-up time, and there was a threshold effect.

Keywords: Ultrasound (US); microwave ablation (MWA); benign thyroid nodules (BTNs); different composition; volume reduction ratio (VRR)

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Introduction

The incidence of thyroid nodules has increased annually. The proportion of thyroid nodules detected by ultrasound (US) is as high as 70%, of which 90% are benign nodules (1). Most benign nodules have no obvious clinical symptoms and follow-up observations are required. However, patients seek treatment for some nodules because of their large size or special location, causing local compression symptoms or affecting aesthetics. Traditional clinical treatment involves surgery (2,3). Although thyroid nodule resection can completely remove lesions, there are problems such as surgical trauma, neck scars that affect appearance, and other postoperative complications (4).

US-guided thermal ablation (TA) can be performed under local anesthesia with percutaneous needle penetration, which is less traumatic to the tissue and does not affect aesthetics; the US instrument monitors and guides in real time during the operation, which can avoid damaging blood vessels, nerves, and other tissues, thus reducing the incidence of postoperative complications. Currently, US-guided TA for the treatment of benign thyroid nodules (BTNs) is recommended by several guidelines (3,5,6).

Microwave ablation (MWA) is a type of TA. Compared with other TA methods such as radiofrequency ablation and laser ablation, it has the advantages of a strong coagulation ability, and a large ablation zone, and has become a promising therapeutic method (7-10). In addition, most studies have shown that MWA is effective in the treatment of BTNs; however, there are large individual differences in the degree of lesion absorption and shrinkage speed. Although the internal components of nodules have been reported as important influencing factors, most inferences have been made from timepoint studies, such as comparing the volume reduction ratio (VRR) at 1, 3, 6, and 12 months (11-14). Few studies have reported temporal changes in the VRR in BTNs of different compositions (15). Therefore, this study evaluated the efficacy of US-guided MWA in BTNs of different compositions, analyzed temporal changes in the VRR, and determined when the VRR increases most significantly. We present this article in accordance with the STROBE reporting checklist (16) (available at https://qims.amegroups.com/article/view/10.21037/qims-24-2096/rc).

Methods

Patients

This is a retrospective study. We consecutively collected patients with BTNs of different compositions that underwent US-guided MWA between July 2020 and June 2021 in The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital. Patients with BTNs performed MWA because of their large size or special location, causing local compression symptoms or affecting aesthetics. To protect patient privacy, all patients' details were de-identified. The inclusion criteria were as follows: (I) the US examination showed that the thyroid nodule was benign, namely Chinese Thyroid Imaging Reporting and Data System 3 categories (no obvious hypoechoic signal, vertical orientation, lobulated or irregular margin, and microcalcification) and (II) fine-needle aspirations or core needle biopsy confirmed that the nodules were benign, namely Bethesda II (17). The exclusion criteria were as follows: (I) cystic thyroid nodules or (II) lack of complete US data. BTNs were classified into three categories: predominantly cystic (51–90% fluid), predominantly solid (11–50% fluid), and solid (≤10% fluid). Schematic diagrams are shown in *Figure 1*. A total of 221 treatment effective nodules (216 patients) were included in this study. Among the effective nodules, 21 were predominantly cystic, 61 were predominantly solid, and 139 were solid. This study was conducted in accordance with the tenets of the Declaration of Helsinkiand its subsequent amendments (18). This retrospective study was approved by the Ethics Committee of The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital (No. 20220802018), and informed consent was obtained from all patients prior to the procedure.

Equipment and operational tools

US, contrast-enhanced ultrasound (CEUS), and US-guided MWA were performed using MyLab Twice (Esaote, Genoa, Italy). A linear array probe (LA533) with 4.0–13.0 MHz was used for US and CEUS examinations. An MTI-5A MWA therapy instrument (Nanjing Changcheng Medical Equipment, Nanjing, China) was used for MWA, including a microwave generator (frequency 2,450 MHz, output power 30 W), microwave cable, and XR-A1610W liquid-cooled circulation MWA needle (diameter 16 G, length 10 cm). For predominantly cystic nodules and predominantly solid nodules, a 20 mL syringe was used to extract cystic fluid.

CEUS of nodules was performed using 1.5 mL of SonoVue (Bracco Imaging, Milan, Italy).

US and CEUS examination

CEUS of nodules was performed using 1.5 mL of SonoVue.

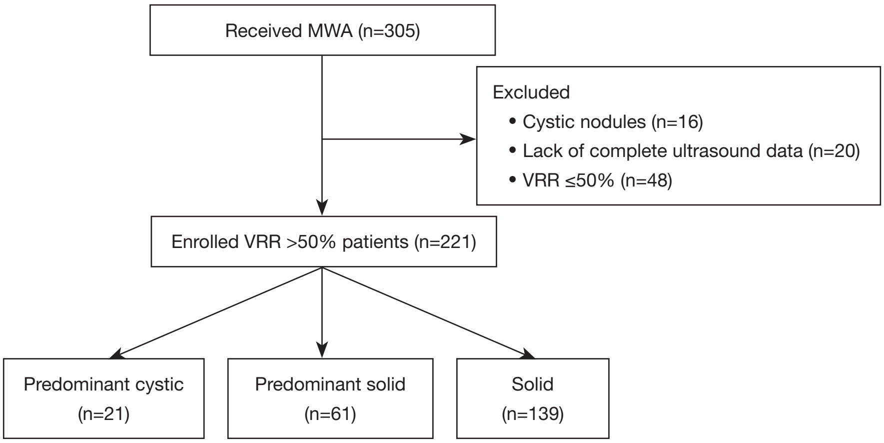

Figure 1 Flow chart of BTNs selection. BTNs, benign thyroid nodules; MWA, microwave ablation; VRR, volume reduction ratio.

US, CEUS and MWA were performed by two physicians with 7-year experience in thyroid interventional US. Conventional transverse and longitudinal images of each target nodule were obtained using US. The volume of the nodule was calculated using the following equation based on diameter measurement with US: $V= \pi abc/6$ (V: volume; a: the largest diameter; b and c: the other two perpendicular diameters). Dynamic CEUS examinations were then performed for each BTN. BTNs were observed continuously for 2 min to determine their enhancement range. After US-guided MWA, CEUS was again performed to evaluate the ablation effect. The lesion was not completely ablated if there was an area of enhancement. Supplemental ablation was required until CEUS showed no enhancement of the lesion. The US data and characteristics of each BTN were collected after MWA. All detection data were stored for subsequent analysis.

Ablation technique

The patient was placed in a supine position with the neck fully exposed. After routine disinfection and draping, the patient was locally anesthetized with 2% lidocaine hydrochloride at the puncture site, puncture route, and anterior thyroid capsule under US guidance. Multiple injections of 0.9% normal saline were used to form a liquid isolation zone around the thyroid tissue (large blood vessels, nerves, trachea, esophagus, and muscles) with a width of approximately 5–10 mm to avoid puncture and ablation damage to the surrounding tissue. The 16-G MWA needle punctured through the isthmus to the inside of the BTN. The "moving shot technique" was used to perform ablation from inside to outside (deep to shallow) (7-10), until the nodules were completely covered by the hyperechoic gasification area. Before ablation, in predominantly cystic nodules and predominantly solid nodules, cystic fluid was aspirated as much as possible, after which the solid portion and cyst wall were ablated. MWA was performed directly for solid nodules. If there were multiple nodules in the thyroid gland at the same time, each nodule was ablated separately. After MWA, CEUS was performed to evaluate the ablation effect. Before completing the MWA of a BTN, the MWA needle remained inserted within the nodule. The following data were recorded: ablation time, energy, and possible complications such as hoarseness, hematoma, and pain.

Data collection and follow-up evaluation

The following data were recorded before and after MWA: (I) data and characteristics of each BTN using US examination, including size, nodule position, proximity to the trachea or recurrent laryngeal nerve, shape, margin, nodular composition, and homogeneity; (II) side effects; (III) VRR at the 12-month follow-up. VRR was calculated as follows: VRR = (initial volume − follow-up volume)/initial volume ×100%. A VRR >50% within 12 months was considered effective and a VRR ≤50% was considered ineffective (19).

Statistical analysis

All analyses were performed using EmpowerStats statistical software (X&Y Solutions, Boston, MA, USA). Demographic and US characteristics were compared between the effective and ineffective groups. Continuous variables were compared using the Mann-Whitney *U* test, and categorical variables were compared using Fisher's exact test. Continuous data were described as median (25th percentile, 75th percentile) and categorical variables as frequencies and percentages. Moreover, we used a generalized additive mixed model to identify non-linear relationships. If a non-linear correlation was observed, a two-piecewise linear regression model was used to calculate the threshold effect of time on VRR in terms of the smoothing plot. When the ratio between the VRR and time appeared obvious in the smoothed curve, the recursive method calculated the inflection point and the maximum model likelihood was used (20). Intraclass correlation coefficient (ICC) was used to evaluate the consistency of two operators in MWA of BTNs. Statistical significance was set at P<0.05.

Results

Baseline characteristics

A total of 645 examinations were performed in 216 patients. The mean examination ± standard deviation in each patient was 2.92±0.85. The baseline characteristics of the nodules included in this study are shown in *Table 1*.

Follow-up results

The relationship between VRR and time was non-linear and had a threshold effect, with the thresholds (inflection points) of VRR growth at 2.0, 2.3, and 4.3 months for predominantly cystic, predominantly solid, and solid nodules, respectively. In predominantly cystic nodules, the VRR increased by 36% per month until 2.0 months (P<0.001) and by 1.4% per month after 2.0 months (*Figure 2A*). In predominantly solid nodules, the VRR increased by 30.6% per month until 2.3 months (P<0.001) and by 0.7% per month after 2.3 months (*Figure 2B*). In solid nodules, the VRR increased by 17.4% per month until 4.3 months (P<0.001) and by 0.3% per month after 4.3 months (*Figure 2C*). Threshold effect for the relationship of follow-up time with VRR using piece-wise linear regression as shown in *Table 2*. There was no significant difference in inflection points among the three groups (P=0.37). The differences in VRR changes were statistically significant among the three groups (P<0.001).

Figure 3 illustrates the US images of each group of nodes before MWA and with VRR >50%, respectively.

Consistency between the two operators

ICC was 0.839 (95% confidence interval: 0.773, 0.887), indicating good consistency between the two operators in MWA of BTNs.

Discussion

Clinical observation without intervention is an option for most BTNs, but appropriate treatment should be administered when the nodule has recently grown rapidly, is affecting aesthetics or causing symptoms of pressure, and if the patient is in a state of anxiety due to the nodule (21). Surgery is an effective treatment modality for BTNs. However, surgical procedures have shortcomings such as high trauma, possible serious complications, and damage to thyroid function, and need to be performed under general anesthesia; therefore, there is a clinical need for a minimally invasive, safe, and effective treatment modality (1,22).

US-guided MWA has become the first-line treatment modality for BTNs in recent years as it is minimally invasive, safe, and effective (3,5,23). The theory behind MWA for BTN is that polar molecules in human tissues are shocked by ultra-high frequency electromagnetic waves and high temperatures is generated within a short period of time, causing coagulative necrosis in the target tissues. The resulting necrotic tissues are eventually cleared and absorbed by the body's immune system to form a physical local inactivation for treatment purposes (5).

For predominantly cystic or predominantly solid nodules, although US-guided chemical ablation is a minimally invasive treatment modality that can be applied, energy-based MWA can achieve better treatment outcomes (11). Previous studies have identified different internal nodule components as important factors affecting nodule shrinkage rates (5,11). However, there are few reports on temporal changes in the VRR in BTNs with different compositions. Therefore, in this study, BTNs were divided into predominantly cystic, predominantly solid, and solid nodules to explore how the VRR changes over time (7-10).

Figure 2 shows that the temporal changes in VRR for BTNs with different components are different. Previous studies on VRR mostly include timepoint studies, such as at 1, 3, 6, and 12 months (11,12). Few studies have reported how the VRR changes over time in BTNs with different compositions. In addition, in actual clinical practice, although the patient can be followed up by thyroid US, it

Table 1 Baseline characteristics of the nodules included in this study

Characteristics	Predominantly cystic nodules	Predominantly solid nodules	Solid nodules	Total
Number of cases	21	61	139	221
Volume (mL)				
Median (25th percentile, 75th percentile)	3.5 (1.6, 9.4)	5.7 (2.8, 11.9)	3.7 (1.6, 7.9)	4.6 (1.8, 9.0)
Mean	6.9	8.2	6.1	6.8
Minimum	0.2	0.1	0.1	0.1
Maximum	34.0	32.9	53.7	53.7
Position (n)				
Left lobe	15	22	59	96
Right lobe	5	39	76	120
Isthmus	1	0	4	5
Location, close to trachea (n)				
No	6	25	67	98
Yes	15	36	72	123
Location, close to recurrent laryngeal nerve (n)				
No	9	30	79	118
Yes	12	31	60	103
Shape (n)				
Regular	14	45	120	179
Irregular	7	16	19	42
Margin (n)				
Circumscribed	14	51	116	181
Not circumscribed	7	10	23	40
Homogeneity (n)				
Homogeneous	2	8	16	26
Heterogeneous	19	53	123	195

can be difficult to access the patient at the timepoint specified by the doctor due to factors like patient compliance, disease severity, and public health measures [such as those seen during the coronavirus disease 2019 (COVID-19) pandemic]. Therefore, this study adopted a method more suitable for the actual clinical situation; that is, the generalized additive mixed model, which can be used to analyze changes in VRR over time and is not limited by specific timepoints. The log-likelihood ratio test, using a piecewise regression model for comparison, revealed the existing threshold.

In this study, the VRR of BTNs with three different components first increased significantly and then tended to increase slowly, which is consistent with the efficacy of radiofrequency ablation and Laser photocoagulation in the treatment of BTNs (7,8,19). The VRR of predominantly cystic nodules was significantly higher than that of the other two groups in the first few months and at 12 months, which is consistent with the conclusions of Khanh *et al.* and Fu *et al.* (13,15). Predominantly cystic nodules showed the most significant increase in VRR at 0–2.0 months, whereas

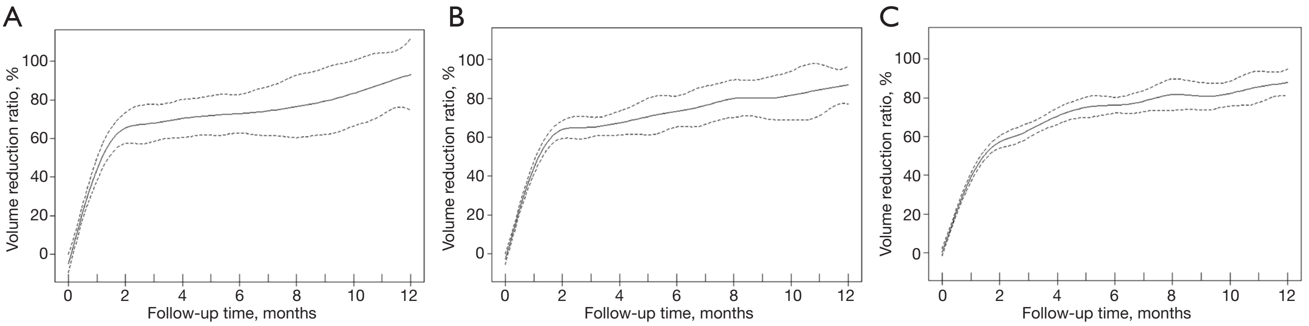

Figure 2 VRR during the follow-up period. The abscissa represents time and the ordinate represents VRR. The solid line in the middle is the fitted line, and the dashed lines on both sides are the 95% confidence intervals. (A) Temporal changes in VRR in predominantly cystic nodules. (B) Temporal changes in VRR in predominantly solid nodules. (C) Temporal changes in VRR in solid nodules. VRR, volume reduction ratio.

Table 2 Threshold effect for the relationship of follow-up time with VRR using piece-wise linear regression

Categories	β (95% CI)	P
VRR in predominant cystic group		
Time ≤2.0 m	36.0 (28.8, 43.2)	<0.001
Time >2.0 m	1.4 (−1.0, 3.7)	0.26
Log-likelihood ratio test	–	<0.001
VRR in predominant solid group		
Time ≤2.3 m	30.6 (27.3, 33.9)	<0.001
Time >2.3 m	0.7 (−0.5, 2.0)	0.25
Log-likelihood ratio test	–	<0.001
VRR in predominant solid group		
Time ≤4.3 m	17.4 (16.2, 18.5)	<0.001
Time >4.3 m	0.3 (−1.3, 3.6)	0.63
Log-likelihood ratio test	–	<0.001

CI, confidence interval; m, month; VRR, volume reduction ratio.

predominantly solid nodules and solid nodules showed the most significant increases at 0–2.3 and 0–4.3 months, respectively. The most significant increase in VRR was found in predominantly cystic nodules, likely because the proportion of cystic components was greater than 50%. Before MWA, cystic fluid was extracted, and MWA was performed on the solid portion and cystic wall. After the operation, the nodule volume was significantly reduced compared with that before the operation; however, the VRR calculation was based on the data before the operation, and thus, the VRR increased faster (24,25). Predominantly solid nodules had the second highest VRR, possibly due to the cystic component accounting for ≤50%. The proportion of cystic components was lower than that of predominantly cystic nodules, and the proportion of solid components was higher. Compared to predominantly cystic and predominantly solid nodules, solid nodules had the slowest VRR, and the reasons for this may be as follows. First, it is extremely clear that MWA easily overcame smaller remnant solid portions compared to larger solid portions of the completely solid nodules. Second, solid nodules are ablated at multiple levels during the ablation process (which may affect the operator's field of view), the timing of nodule ablation may be inaccurate, and the ablation needle may not ablate at each level of the nodule for the right amount of time. If the ablation is not sufficient, the nodule is not completely inactivated, and the treatment effect is not significant (26). If ablation is excessive, it may cause carbonization, and carbonized tissue is usually difficult to absorb, thus showing a slow shrinkage of the nodule after treatment (27). This study will help to explore the pattern of shrinkage of BTNs of different compositions after US-guided MWA therapy, which will help to explain to patients in clinical practice that the shrinking process of nodules of different compositions is not analogous.

There are certain limitations in this study. First, this was a retrospective study with inevitable bias. Second, this study was not a timepoint study due to compliance and time constraints of the follow-up population; however, this study used the generalized additive mixed model to fit the VRR data at different time points and calculated the thresholds. Third, similar to various studies on MWA and radiofrequency ablation, we could not histologically

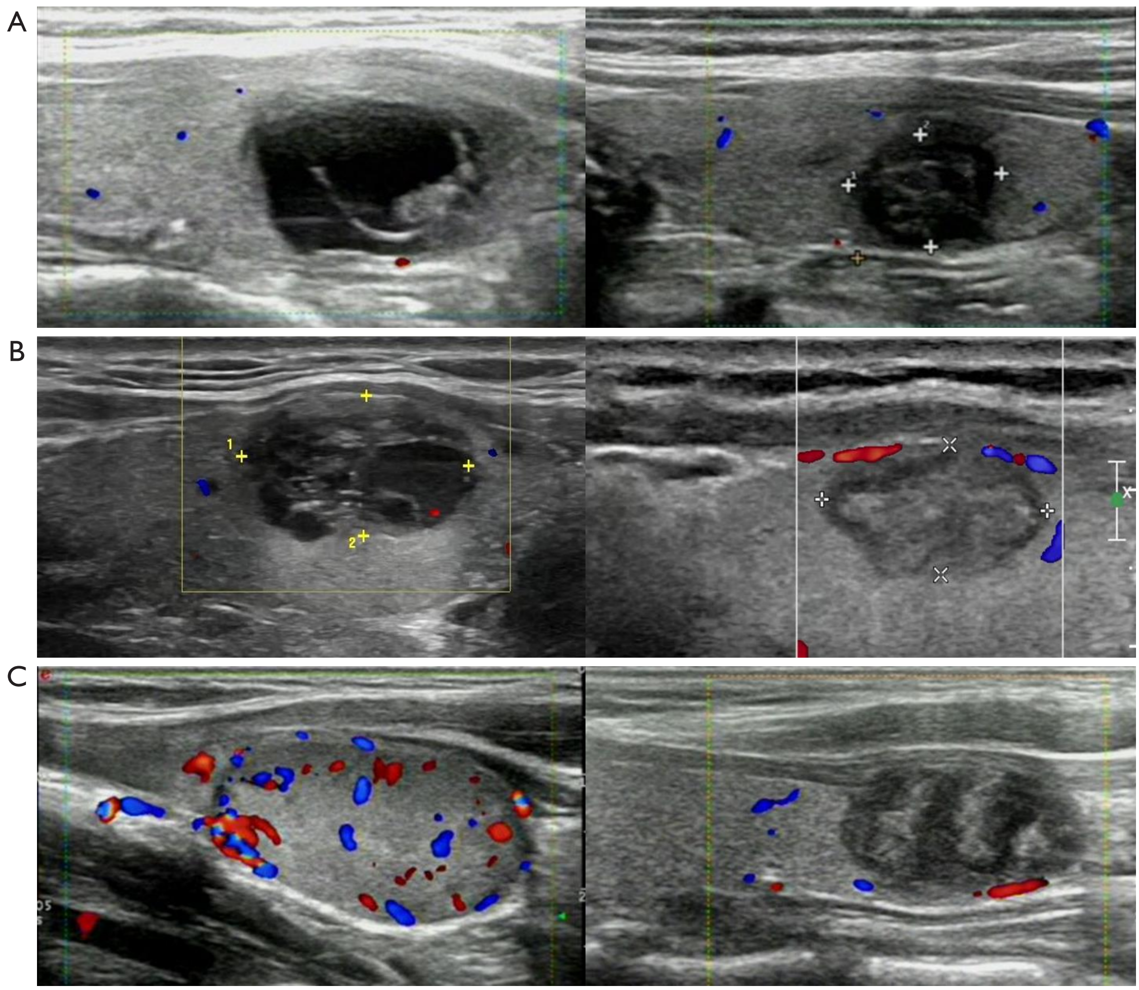

Figure 3 Ultrasound images of the three different components of the nodules before MWA and with VRR >50%. Left and right panels are longitudinal color Doppler flow images of the nodes before and after MWA, respectively. (A) A 55-year-old female with a predominantly cystic nodule in the left lobe measuring 20 mm × 19 mm × 16 mm and approximately 3.2 mL in volume before MWA and approximately 13 mm × 10 mm × 10 mm and 0.7 mL in volume 2 months after MWA, with a VRR of 78%. (B) A 56-year-old male with a predominantly solid nodule in the right lobe measuring 19 mm × 15 mm × 12 mm with a volume of approximately 1.8 mL before MWA and approximately 15 × 10 × 8 mm with a volume of approximately 0.6 mL 2 months after MWA, with a VRR of 67%. (C) A 23-year-old female with a solid nodule in the left lobe measuring 27 mm × 20 mm × 15 mm and approximately 4.2 mL in volume before MWA and approximately 18 mm × 13 mm × 10 mm and 1.2 mL in volume 3 months after MWA, with a VRR of 71%. MWA, microwave ablation; VRR, volume reduction ratio.

confirm BTNs without surgery. Fourth, this study did not compare the efficacy of MWA with other treatments like ablation and ethanol ablation for treating thyroid nodules. Fifth, we noted that the best tool to calculate these volumes of predominantly cystic nodules and predominantly solid nodules was CEUS, compared to conventional ultrasonography. In future research, we will use CEUS to calculate the enhanced remnant solid portion after aspiration of nodule's fluid for the partially liquid BTNs.

Conclusions

In the present study, the VRR after US-guided MWA for different components of BTN was non-linearly related with the follow-up time, and there was a threshold effect. The VRR of BTNs of three different compositions after MWA increased with time. The rate of growth was most significant before the threshold and demonstrated a slow growth after the threshold.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-2096/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-2096/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the tenets of the Declaration of Helsinki and its subsequent amendments. This retrospective study was approved by the Ethics Committee of The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital (No. 20220802018), and informed consent was obtained from all patients prior to the procedure.

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