Clinical efficacy of ethanol ablation and microwave ablation on cystic or predominantly cystic thyroid nodules: A retrospective comparative study

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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: Clinical data of patients with cystic or predominantly cystic thyroid nodules intervened with EA or MWA in the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine from January 2013 to November 2019 were retrospectively analyzed. The patients were divided into EA group (n=30) and MWA group (n=26). The volume and volume reduction rate of thyroid nodules before ablation, and at 3 months and 12 months after ablation were compared between the two groups. The effective rate and incidence of adverse events in both groups were recorded.

Results: The median volume reduction rate at 3 months after ablation was significantly higher in EA group than MWA group (81.30% vs. 75.76%, P=0.010), while no significant difference was detected at 12 months (93.39% vs. 89.34%, P=0.141). There was no significant difference in effective rate between the two groups during the follow-up (P>0.05). The maximum diameter of the thyroid nodule (2.96 ± 0.78 cm vs. 3.78 ± 1.02 cm, P<0.05), mean volume of thyroid nodule (4.92 [2.93-10.19] ml vs. 8.33 [4.92-15.02] ml, P<0.05) and medical cost (111.73 ± 55.22 USD vs. 2443.79 ± 285.46 USD, P<0.001) were significantly lower in EA group than 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). 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. Although EA is more cost-effective, it requires more times of treatment and may poses a higher risk of postoperative pain compared with MWA.

Introduction

The incidence of thyroid nodules is increasing annually as they are frequently detected. Surgery is a preferred management for thyroid nodules, although it has limitations like large trauma, permanent postoperative scars, risk of complications, and long-term postoperative medication. At present, ultrasound-guided minimally invasive treatment for thyroid nodules is becoming increasingly 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 the treatment of 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]. 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 [2]. The efficacy of thermal ablation in the treatment of benign thyroid nodules has been confirmed, mainly including the laser ablation (LA), radio frequency ablation (RFA), microwave ablation (MWA) and high-intensity focused ultrasound (HIFU). In 2009, Beak et al. [3] have 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 [4]. Therefore, MWA has been regarded as an effective treatment for benign thyroid nodules [5].

Though both EA and MWA are effective in the treatment of cystic thyroid nodules, the comparison of their efficacy and treatment is scant. 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

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. Patients with cystic or predominantly cystic thyroid nodules intervened with EA or MWA in our hospital from January 2013 to November 2019 were retrospectively recruited. They were divided into EA group (n = 30) and MWA group (n = 26). Baseline characteristics, and the volume and ultrasound characteristics of thyroid nodules before ablation, and at 3 months and 12 months after ablation were recorded for analyses. Ultrasound images of all thyroid nodules were retrospectively reviewed and scored using the 2021 Korean Thyroid Imaging Reporting and Data System and Imaging of Korean Society of Thyroid Radiology (K-TIRADS) [6].

Inclusion and exclusion criteria

Inclusion criteria: (1) Benign thyroid nodules with the cystic (CYS, cystic component ≥ 75%) or predominantly cystic component (M-CYS, 50% < cystic component < 75%) examined by ultrasonography; (2) Thyroid nodules with Bethesda category II classified by the Bethesda system for reporting thyroid cytology (TBSRTC) based on ultrasound and cytological findings [7]; (3) Patients with clinical symptoms and signs of local compression, hoarseness and cosmetic concern; (4) No history of radiotherapy, surgery for neck cancers, malignancies and metastatic lymph nodes; (5) Patients requested for interventional treatment after informed consent or refused to surgery.

Exclusion criteria: (1) Contralateral vocal cord dysfunction; (2) Allergy to medications used in the present study; (3) Severe bleeding tendency or abnormal coagulation function; (4) Systemic infection, high fever, or leukocyte disorder; (5) Severe organ dysfunction; (6) Pregnant and lactating women.

Ablation procedure

The patient was in the supine position with the neck fully exposed. After disinfection using 0.2% iodine and paving sterile sheets, ultrasound-guided local infiltration anesthesia using 1% lidocaine was performed in the lesion site. Normal saline was continuously injected in the space between 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 microwave ablation. Then a 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. MWA was completed until ultrasound confirmed that there was no obvious blood flow in the thyroid nodule. In EA group, cystic fluid was aspirated as much as possible, and 98% alcohol was injected into the thyroid nodule under the guidance of ultrasound for 3 times of irrigation. Absolute alcohol corresponded 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 months and 12 months after ablation, and ER were calculated using the following equations. V (ml) = $\pi abc/6$, where a, b and c were the three maximum perpendicular diameters shown on the ultrasound image. VRR (%) = (preoperative V – postoperative V) / preoperative V × 100%. Effective rate (ER) (%) = case number of success treatment with VRR ≥ 50% - total case number × 100%.

Statistical analysis

Statistical analysis was performed using SPSS 24.0. Normally distributed measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$), 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

A total of 56 patients with cystic or predominantly cystic thyroid nodules were recruited, involving 30 patients (mean age, 45.87 ± 12.95 years) in EA group and 26 (mean age, 40.15 ± 16.14 years) in MWA group. There were 3 male and 27 female patients in EA group, and 1 male and 25 female patients in MWA group. The maximum diameter of the thyroid nodule (2.96 ± 0.78 cm vs. 3.78 ± 1.02 cm, $P < 0.05$), mean volume of thyroid nodule (4.92 [2.93–10.19] ml vs. 8.33 [4.92–15.02] ml, $P < 0.05$) and medical cost (111.73 ± 55.22 USD vs. 2443.79 ± 285.46 USD, $P < 0.001$) were significantly lower in EA group than 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 two groups, there was significant differences in the K-TIRADS classification ($P = 0.009$) (Table 1).

Table 1
Baseline characteristics of patients with cystic or predominant cystic thyroid nodules (n = 56).

Characteristic	EA group	MWA group	*P* value
Patients/nodules (n)	30/30	26/27	
Male/female (n)	3/27	1/25	
Cystic component			
≥ 75% (CYS)	18 (60%)	8 (29.63%)	
50–75% (M-CYS)	12 (40%)	19 (70.37%)	
Age (years)	45.87 ± 12.95	40.15 ± 16.14	0.144
Maximum diameter (cm)	2.96 ± 0.78	3.78 ± 1.02	0.001
Volume (ml)	4.92 (2.93–10.19)	8.33 (4.92–15.02)	0.027
K-TIRADS classification	2 (2–2)	2 (2–3)	0.009
Treatment cycle	2.5 (1.0-3.3)	1 (1–1)	0.000
Medical cost (USD)	111.73 ± 55.22	2443.79 ± 285.46	0.000

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

Overall therapeutic efficacy

The median V before ablation and 3 months and 6 months after ablation in EA group was 4.92 ml, 0.86 ml, and 0.39 ml, respectively, which was 8.33 ml, 1.99 ml, and 1.01 ml in MWA group, respectively. Postoperative V was significantly reduced compared with that of baseline in both groups (all $P < 0.001$) (Table 2, Fig. 1). VRR at 3 months after ablation was significantly higher in EA group than MWA group (81.30% vs. 75.76%, $P = 0.010$), while no significant difference was detected at 12 months (93.39% vs. 89.34%, $P = 0.141$) (Table 2, Fig. 2A). However, no significant differences in ER at both 3 months (90.00% [27/30] vs. 81.48% [22/27], $P = 0.354$) and 12 months after ablation (100% [30/30] vs. 96.30% [26/27], $P = 0.218$) were detected between groups (Fig. 2B).

Table 2
EA and MWA outcomes after ablation in patients with cystic or predominant cystic thyroid nodules (n = 56).

		Baseline	3 months	12 months
EA group (n = 30)	V (ml)	4.92 (2.93–10.19)	0.86 (0.44–1.65)[a]	0.39 (0.08–0.88)[a]
	VRR (%)	-	81.30 (74.46–90.96)	93.39 (81.28–97.67)[b]
MWA group (n = 26)	V (ml)	8.33 (4.92–15.02)	1.99 (1.39–4.07)[a]	1.01 (0.42–1.49)[a]
	VRR (%)	-	75.76 (56.19–80.84)	89.34 (81.61–93.91)[b]

EA = ethanol ablation; MWA = microwave ablation; V = volume; VRR = volume reduction rate. [a]P<0.001 vs. Baseline; [b]P<0.001 vs. 3 months.

The age, and V and VRR of thyroid nodules were introduced into the logistic and linear regression analysis identify potential influencing factors for the efficacy of ablation, which showed that age was significantly correlated with VRR at 12 months after ablation (t = 2.30, P = 0.025) (Table 3).

Table 3
Influencing factors for VRR and ER.

	VRR at 12 months		ER	
	Liner regression		Logistic regression	
	t	*P* value	OR (95%CI)	*P* value
Age	2.30	0.025	1.16 (0.93–1.43)	0.189
Volume	-0.01	0.990	1.43 (0.59–3.47)	0.435
Max diameter	0.91	0.366	6.81 (0.22-211.83)	0.274

VRR = volume reduction rate; ER = effective rate; OR = odds ratio; CI = confidence interval.

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 8 (29.63%) CYS thyroid nodules in EA and MWA group, respectively. A total of 12 (40.00%) and 19 (70.37%) M-CYS thyroid nodules were detected 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, while the significant difference was only detected at 12 months after EA (94.80% vs. 86.14%, P = 0.038). 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 4).

Table 4

VRR of cystic and predominant cystic thyroid nodules

	VRR at 3 months		VRR at 12 months	
	CYS (≥ 75%)	M-CYS (50–75%)	CYS (≥ 75%)	M-CYS (50–75%)
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	78.76 (69.03–87.21)	72.74 (48.15–79.67)	92.83 (90.06–96.57)	84.13 (76.10-93.91)
P value	0.120	0.240	0.405	0.871

VRR = volume reduction rate; EA = ethanol ablation; MWA = microwave ablation; CYS = cystic; M-CYS = predominantly cystic. *P< 0.05 vs. CYS group.

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 of EA group (8 [26.67%] vs. 6 [23.08%], P = 0.757), which were relieved within one week without the use of analgesics. All patients were well tolerant to EA or MWA, and hematoma, hoarseness, facial paralysis, and local infection were not reported.

Discussion

Thyroid nodules are common, with the overall prevalence of 36.9% in the Chinese population [8]. In recent years, the detection rate of thyroid nodules is up to 68% with the widespread application of ultrasonography [9]. Only 5–10% of thyroid nodules are malignant, and the majority are benign that need no clinical treatment until the occurrence of compression or cosmetic concerns [10, 11]. Currently, the efficacy and safety of EA and thermal ablation on cystic or predominantly cystic thyroid nodules have been validated [1, 2, 12–14].

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 tumor shrink. However, the recurrence rate remains high after EA for predominantly cystic nodules, and the efficacy of multi-injection of alcohol is controversial [15]. Generally speaking, the number of alcohol injection is determined by the initial volume of the tumor, treatment response and follow-up findings, and most cases require 2–3 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 8 patients (26.67%) complained of mild pain, which were slightly higher than 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. VRR of cystic thyroid nodules after EA was significantly higher than that of predominantly cystic ones. Our previous study has reported the 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 [16]. 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 (PTMC), and primary hyperparathyroidism (PHPT) [4, 17, 18]. The median VRR of benign thyroid nodules at 6 months and 12 months of MWA reaches 75.9% and 86.67%, respectively [4]. However, the efficacy of MWA on cystic or predominantly cystic thyroid nodules remains unclear. In the present study, the median VRR at 3 months and 12 months of MWA was 75.76% and 89.34%, respectively. Luo et al. [14] 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 significantly shrank cystic or predominantly cystic thyroid nodules. VRR and ER were higher in EA group during the follow-up period than those of MWA group, although significant difference was only detected in VRR at 3 months after ablation. The higher ER of EA group may be attributed to the significantly smaller volume of thyroid nodules at baseline compared with that of MWA group. Previous evidence has supported the negative correlation between the therapeutic efficacy of ablation and initial volume of nodules [19, 20]. Currently, the comparison between the clinical efficacy of EA and MWA has been rarely reported. Liu et al. [21] reported the similar efficacy of EA and MWA on simple thyroid cysts, although the incidence of intraoperative pain was lower in MWA group than that of EA group. Zhou et al. [22] demonstrated the superb efficacy of MWA with less damage in treating benign solid-cystic thyroid nodules compared with that of EA. The combination of EA and MWA has been proposed in a latest study, which is reported to significantly shorten the procedure time and reduce the recurrence in patients with predominantly cystic thyroid nodules [23]. In the present study, we compared VRR of cystic and predominantly cystic thyroid nodules after EA and MWA, which was higher in EA, although no significant difference was obtained. Moreover, ER was comparable between EA and MWA group either in cystic or predominantly cystic thyroid nodules.

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

Declarations

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 obtained from all patients by telephone.

Consent for publication

Not applicable.

Availability of data and materials

Datasets generated in this study are available on request to the corresponding author.

Competing interests

The authors declare that they have no competing interest.

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Author contributions

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 the diagnosis. Shuhang Xu and Xiaoqiu Chu performed microwave ablation and ethanol ablation. Yueting Zhao and Xue Han were responsible for the perioperative management. Shuhang Xu, Xiaoqiu 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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Figures

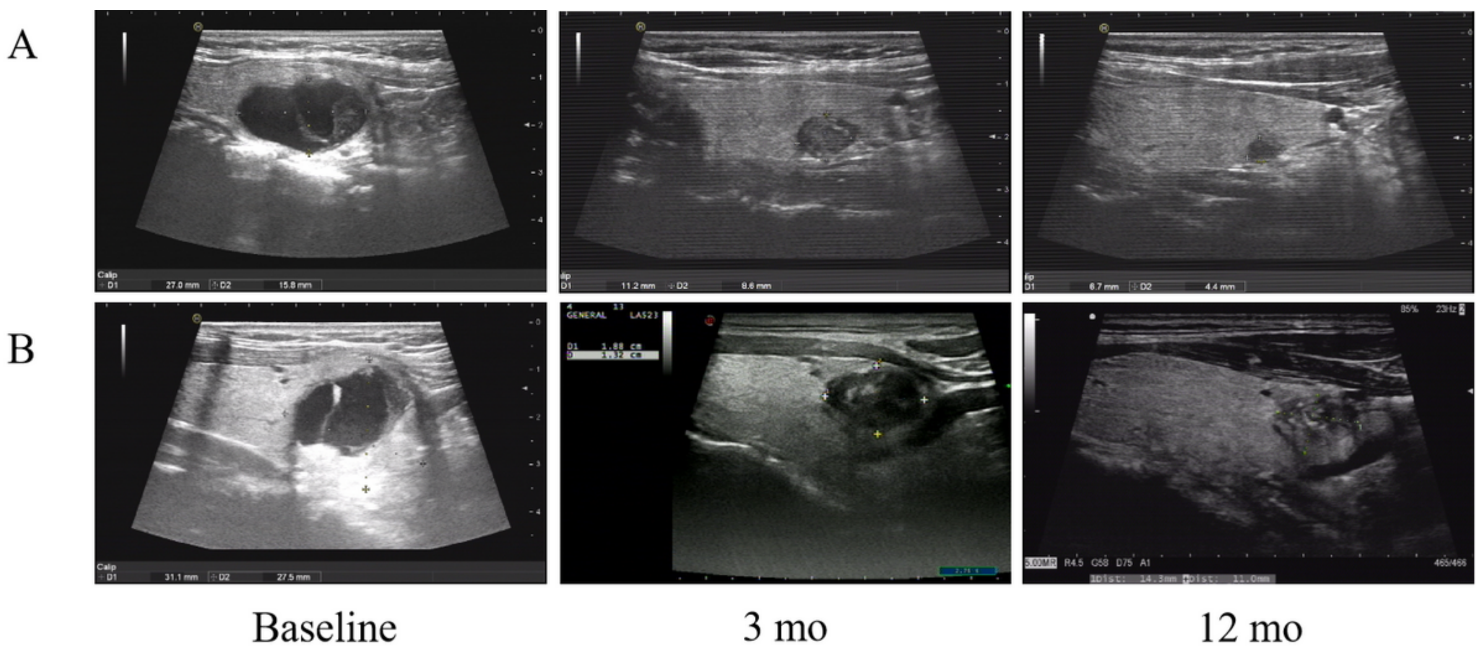

Figure 1

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 month and 12 months after ablation. B. A 45-year-old male patient with the volume of thyroid nodule before MWA of 11.39ml, which was reduced to 2.07 ml (VRR = 81.84%) and 0.66 ml (94.22%) at 3 and 12 months after ablation.

EA = ethanol ablation; MWA = microwave ablation.

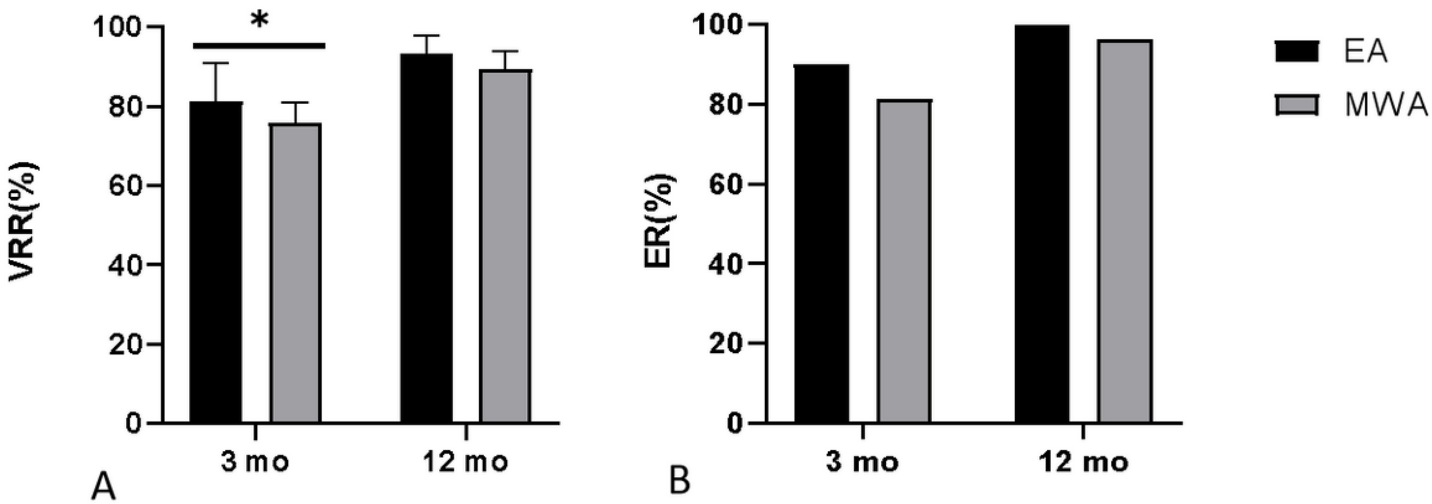

Figure 2

EA and MWA outcomes. A. VRR at 3 months and 12 months after EA and MWA; B. ER at 3 months and 12 months after EA and MWA.

EA = ethanol ablation; MWA = microwave ablation; VRR = volume reduction rate; ER = effectiveness rate. **P*<0.05.