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Innovative Techniques for Image-Guided Ablation of Benign Thyroid Nodules: Combined Ethanol and Radiofrequency Ablation

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In the treatment of benign thyroid nodules, ethanol ablation (EA), and radiofrequency ablation (RFA) have been suggested for cystic and solid thyroid nodules, respectively. Although combining these ablation techniques may be effective, no guidelines for or reviews of the combination have been published. Currently, there are three ways of combining EA and RFA: additional RFA is effective for treatment of incompletely resolved symptoms and solid residual portions of a thyroid nodule after EA. Additional EA can be performed for the residual unablated solid portion of a nodule after RFA if it is adjacent to critical structures (e.g., trachea, esophagus, and recurrent laryngeal nerve). In the concomitant procedure, ethanol is injected to control venous oozing after aspiration of cystic fluid prior to RFA of the remaining solid nodule.

Keywords: *Benign thyroid nodule; Image-guided ablation; Radiofrequency; Ethanol*

INTRODUCTION

Thyroid nodules are relatively common in populations, with 10–41% detected by ultrasonography (US) (1-9). Most thyroid nodules are benign and require no treatment. However, benign nodules are sometimes treated for cosmetic reasons or to relieve symptoms such as swallowing. Although surgery is usually curative, it may result in clinically significant morbidities, including voice change associated with damage to the recurrent and superior laryngeal nerves, hypoparathyroidism, and, more rarely, airway obstruction associated with bilateral vocal cord dysfunction, hematoma, or infection (10, 11). Image-guided ablation methods, including ethanol ablation (EA), OK-432 sclerotherapy, laser ablation (LA), and radiofrequency ablation (RFA), are non-surgical modalities increasingly used to treat benign thyroid nodules (4-7, 12-24).

Current guidelines suggest that the optimal treatment modality for thyroid nodules depends on the solid component of these lesions (7-9, 15, 16, 21, 25). For example, OK-432 sclerotherapy or EA is used for treating cystic nodules, whereas thermal methods such as LA or RFA are preferable for benign solid nodules (6, 16, 17, 22-24). OK-432 is commonly used to treat congenital malformations, plunging ranula, or branchial cleft cysts but not benign thyroid nodules (26). Currently, EA is the recommended first-line treatment for predominantly cystic nodules because it is easier to perform and less expensive than RFA (25). Both RFA and LA are effective for volume reduction of thyroid nodules (2, 6, 22, 23, 27). A recent meta-analysis suggested that RFA appears to be superior to LA in reducing benign solid thyroid nodule volume with lesser number of treatment sessions (28).

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Although EA is effective for cystic thyroid nodules, the recurrence rate after a single session of EA is as high as 38.3% (18), necessitating additional RFA or repeat EA. Several groups have introduced stepwise combinations of EA and RFA to manage nodules with residual unablated areas and resolve residual symptoms. Moreover, concomitant use of EA and RFA may be effective during aspiration of predominantly cystic nodules, where EA is used to control bleeding within the nodule prior to RFA. Although combined EA and RFA has been used to enhance the therapeutic effect of RFA in treating hepatic tumors (29-33), there is no consensus on use of the combination for benign thyroid nodules. This article reviews the three types of combined techniques currently used to treat benign thyroid nodules and discusses the indications, clinical outcomes, and safety of each.

Basic EA and RFA Techniques

EA

Ethanol ablation uses a high concentration (95–99%) of ethanol. The skin is punctured with a 16–21-gauge needle, and the target nodule is approached through the thyroid isthmus to prevent ethanol leakage during the procedure. The method of ethanol instillation depends on the solid component of the nodule (15, 16, 34-36). For a cystic or predominantly cystic nodule, the tip of the needle is inserted into the center of the cyst, as much fluid as possible is aspirated, and then ethanol is injected (16). If the cyst contents are viscous, the fluid is aspirated using a large-bore needle, followed by irrigation with normal saline to remove internal debris and colloid material before ethanol instillation. The volume of ethanol injected is usually 50% of the aspirated fluid volume. After 2 minutes of ethanol retention with the needle in place, the injected ethanol is removed completely and the needle is withdrawn. If a predominantly solid nodule contains a cystic component, the latter is punctured, almost completely aspirated, and an appropriate amount of ethanol is instilled (37). The tip of the needle is subsequently inserted into the solid component of the target nodule, followed by infusion of an appropriate volume of ethanol. That volume is based on nodule size and echogenicity of the solid portion. In treating a purely solid nodule, ethanol is injected directly into the nodule (36, 37). Adequate coverage of the target nodule, as indicated by its echogenicity (called intranodular echo-staining), is achieved by adjusting the injection of ethanol under US guidance. After injection, the needle is rapidly withdrawn.

RFA

Radiofrequency ablation is performed using a generator and internally cooled 7-cm electrodes with an 18-gauge active tip measuring 0.5, 0.7, or 1 cm (2, 5, 7). The RF power and the size of the active tip chosen depend on the size and internal characteristics of the targeted nodule. The initial RF power is usually 30–50 W with a 1-cm active tip, but may be 10 W with a 0.5-cm tip or 20 W with a 0.7-cm tip. If a transient hyperechoic zone does not appear at the tip of the electrode within 5–10 seconds, the RF power on a 1 cm tip is increased at 10 W increments to a maximum of 80 W (30 W with a 0.5 cm tip and 50 W with a 0.7 cm tip). Using a trans-isthmic approach, the electrode is inserted from the isthmus to the lateral aspect of a target nodule. The entire length of the electrode should be visualized to minimize possible complications. Benign thyroid nodules can be treated using the moving-shot technique (2, 38, 39). Given that most nodules are usually ellipsoid in shape, there is little margin between the nodule and the normal thyroid parenchyma. Therefore, a fixed electrode technique, which creates a round ablation zone, is considered unsuitable. For this procedure, the target nodule is divided into multiple small conceptual ablation units and RFA is performed unit-by-unit by moving the electrode. The electrode tip is initially positioned in the deepest and most lateral portion of the nodule, after which it is moved backward to the most superficial and most medial portion, thereby preventing visual disturbances caused by echogenic bubbles. RFA is terminated when all conceptual units of the targeted nodule have been transformed into transient hyperechoic zones.

Combination EA and RFA Technique

Additional RFA for Patients Incompletely Treated after a Single Session of EA

Ethanol ablation has been recommended as the first-line treatment for benign cystic thyroid nodules (12, 13, 15, 16). Retrospective and prospective studies show that the mean reduction in nodule volume after EA for thyroid nodules with large > 90% cystic portions (> 90% of the lesion) ranges from 85 to 98.5% (12, 13, 15, 16). A prospective study showed that EA was superior to RFA in volume reduction and cost-effectiveness (16). EA has also

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been used to treat predominantly cystic thyroid nodules–lesions that are 50–90% cystic. However, after a single EA session, the reduction in volume of these nodules was significantly less than that of the > 90% cystic nodules (78.2% vs. 89.7%) (18, 40). Moreover, the long-term recurrence rate of predominantly cystic nodules is as high as 38.3%, necessitating additional treatment sessions. Reportedly, 5–25% of predominantly cystic thyroid nodules are refractory to EA (13, 41-43). Factors influencing the efficacy of EA are the solid component, initial nodule volume > 10 mL, vascularity of the solid component, and volume of injected ethanol (13, 14, 35, 44-46). Solid components are thought to be more resistant to ethanol, a factor that is independently associated with less volume reduction after EA (46). Greater vascularity of the solid component favors drainage of ethanol. Therefore, the therapeutic efficacy of EA is limited (14, 45, 46).

After EA for a predominantly cystic thyroid nodule, patients whose symptoms are incompletely resolved or who have residual unablated areas with internal vascularity on US may benefit from an additional session of EA or RFA (Table 1). Few studies have assessed the efficacy of repeat EA. Two groups reported efficacies of 20–33.3% after the second session and 10–25% after the third session; thus, the efficacy markedly decreases as the number of sessions increases (41, 47). By contrast, an additional session of RFA is effective and safe for treating incompletely resolved nodules after initial EA treatment (45, 46). Additional RFA resulted in a mean reduction in nodule volume of 92% and significant improvements in symptoms and cosmetic appearance after 6 months, with no major complications (e.g., voice change, infection, or esophageal or tracheal injury) (45). These findings were prospectively verified, showing that patients with recurrent or residual thyroid nodules were effectively treated by additional RFA (46). The 1-month recurrence rate after a single EA session was 33%, with a larger solid component in predominantly cystic nodules being an independent factor for recurrence (46). These findings indicate that EA followed by RFA is a safe and effective combination, as shown by volume reduction and resolution of symptoms, especially in treating predominantly cystic nodules with a substantial solid component (Table 1, Fig. 1).

Additional EA for Residual Unablated Nodules after a Single Session of RFA

Radiofrequency ablation is an effective alternative to surgery for treating benign solid thyroid nodules (3, 4, 6, 7, 17-19, 21, 27, 38, 48, 49). The technical success rate is high (100%), and mean reduction in nodule volume is reportedly 33–58% at 1 month and 51–85% at 6 months (1-3, 38, 50, 51). One study showed a mean reduction in nodule volume of 93.4% after 4 years. These findings indicate that RFA is effective in both reducing nodule volume immediately and producing a durable long-term response (6). A single session of RFA is usually sufficient for volume reduction, resolving symptoms, for cosmesis. However, additional RFA sessions may be required for large (> 20 mL) nodules and for those located close to critical structures (e.g., recurrent laryngeal nerve, trachea, and esophagus) (52, 53) (Table 1). It is technically difficult to completely ablate entire large nodules during a single RFA session. Following shrinkage of previously ablated areas, additional RFA sessions can be performed safely and easily, thus making complete ablation possible. However, even for small nodules located close to critical structures, peripheral residual unablated areas are likely to remain, especially when RFA is performed by less experienced operators.

Table 1. Indications and Technical Tips for Combined Ablation Techniques to Treat Benign Thyroid Nodules

Methods	Indications	Technical Tips
RFA after EA	Incompletely resolved symptoms and residual solid portion after EA, especially in predominantly cystic thyroid nodules	Meticulous targeting of residual, highly vascular, solid portion
EA after RFA	Residual unablated solid thyroid nodules adjacent to critical structures (e.g., trachea, esophagus, and recurrent laryngeal nerve); less experienced operator; residual volume < 5 mL with no vascularity	Complete ablation can be achieved when solid nodules show intranodular echo-staining; caution is required to avoid extrathyroid leakage of ethanol
Concomitant EA and RFA	Internal venous oozing during aspiration of fluid prior to RFA, especially in predominantly cystic thyroid nodules	EA may be less effective than RFA in treating arterial bleeding

EA = ethanol ablation, RFA = radiofrequency ablation

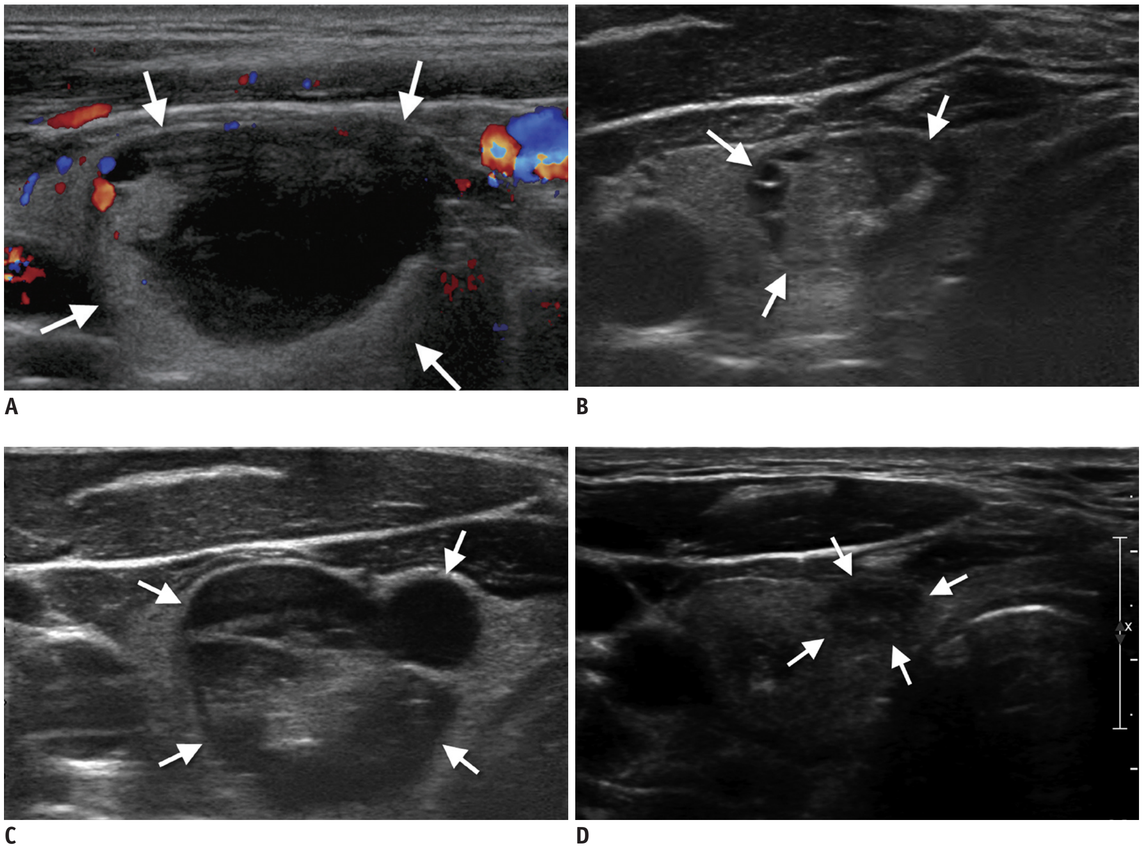

Fig. 1. 57-year-old man with right thyroid nodule.
A. Ethanol ablation of 10.2-mL predominantly cystic nodule (white arrows) showing internal and peripheral vascularity. B. One month after ethanol ablation, volume of nodule (white arrows) was reduced by 88%, to 1.2 mL. C. Three years after ethanol ablation, volume of nodule (white arrows) had gradually increased to 4.9 mL. Recurrent nodule was managed by radiofrequency ablation. D. Three years after radiofrequency ablation, nodule volume (white arrows) was significantly reduced by 98%, and patient's residual symptoms had improved.

Complete ablation is important for preventing recurrence. Nodules undertreated during initial RFA have shown regrowth at their peripheral portions (6), suggesting the need for additional treatment of residual unablated nodules seen on follow-up US.

Ethanol ablation may be an alternative to additional RFA in such cases, as it cannot thermally damage adjacent structures (37). When performed by a less experienced operator (< 20 RFAs/year), the rate of success (defined as the absence of vascular solid components on follow-up US) of a single RFA session was 55.6%, whereas the success rate after additional EA for residual unablated areas was 62.5% (37). As the efficacy of EA is mainly affected by vascularity and the size of the solid component, EA is recommended in patients after incomplete RFA when the remaining component has a volume of ≤ 5 mL and is not highly vascular (13, 14, 35, 37, 44-46). Possible serious complications of EA include leakage of ethanol, causing direct damage to adjacent nerves or critical structures. However, precise US-guided injection and meticulous handling of the injection needle may reduce or prevent complications (Table 1). In a preliminary study, no serious complications after EA were observed, the only adverse effects being transient neck pain and diffuse glandular hemorrhage (37). These findings indicate that RFA followed by EA can be performed safely by personnel less experienced with RFA. This combination may be effective in treating peripheral residual unablated areas caused by technical difficulties or patient discomfort.

Concomitant Ethanol Injection during RFA

Although RFA is successful at treating solid tumors in many organs, a large percentage are difficult to treat or recur locally (29-31, 33, 54-60). For example, RFA has had limited success in treating hepatic tumors > 3 cm and those located near large vessels or the hilum. The region of coagulation necrosis is limited or there may be technical difficulties in optimal positioning of the electrode (29-31, 33, 54, 55, 58-60). The effectiveness of RFA is also limited by the presence of nearby vessels ≥ 3 mm in diameter, which dissipate heat away from target tissues, a phenomenon called the heat-sink effect (29-31, 33, 54, 55, 58-60). The therapeutic effect of RFA may be enhanced by combining it with transcatheter arterial chemoembolization or saline injection. More recently, ethanol injection prior to RFA was introduced for the treatment of hepatocellular carcinomas (32, 33, 56, 59, 60). Compared with RFA alone, this method results in significantly larger areas of coagulation necrosis and a significantly lower energy requirement for coagulation per unit volume of tumor ethanol injection may enhance the therapeutic effects of RFA by destroying tumor vessels and enhancing thermal conduction in tumor tissues, thus reducing the heat-sink effect. Moreover, ethanol heated by RFA may extend the area of tissue necrosis (55, 61).

In contrast to lesions in a large organ such as the liver, complete ablation of a nodule in the relatively small thyroid gland does not require a large area of coagulation necrosis. Rather, ethanol may be instilled to control internal bleeding in predominantly cystic thyroid nodules when aspiration is performed prior to RFA (Table 1). Because decompressed nodules are easier to treat, it is recommended that internal fluid be aspirated before RFA (15, 16, 62-64). However, active bleeding can develop during aspiration due to vessel injury by the aspiration needle or venous bleeding in response to reduced internal pressure (65). This bleeding enlarges the nodule volume, causes a heat-sink effect, and limits the therapeutic effect of RFA. If bleeding is caused by needle injury to feeding arteries in and around the nodule, the bleeding site is usually easily identified and hemostasis can be achieved by RFA (65). However, if venous bleeding from the nodule occurs during aspiration, the bleeding site cannot be identified. Ethanol instillation may then help in controlling internal venous oozing by inducing coagulation necrosis of the cystic wall and thrombosis of microvessels (40, 45, 55) (Table 1). This method has been reported to reduce the total number of treatment sessions to a mean of

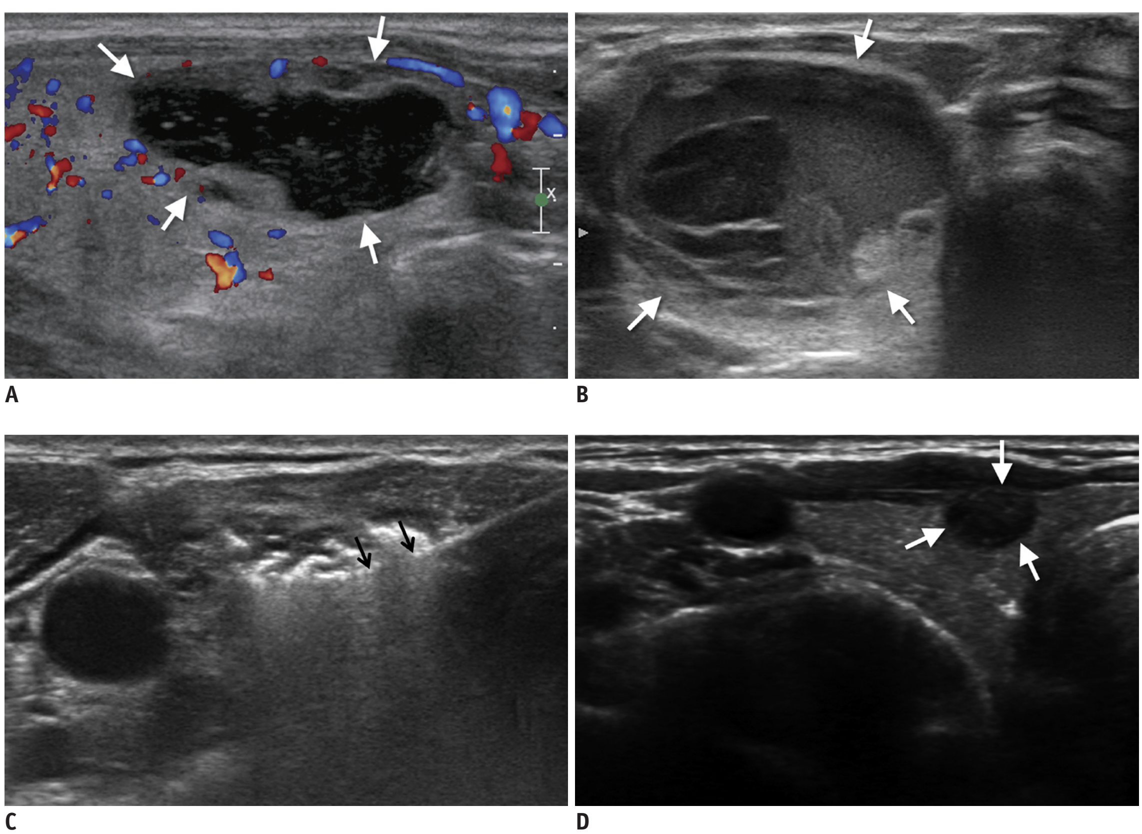

Fig. 2. 65-year-old woman with right thyroid nodule.
A. Ultrasound images showing predominantly cystic mass (white arrows) with increased vascularity, both in internal solid component and periphery. Initial nodule volume was 5.9 mL. **B.** Prior to radiofrequency ablation, internal fluid was aspirated, but nodule (white arrows) increased in size because of internal venous oozing. **C.** After bleeding was controlled by ethanol ablation, radiofrequency ablation was successfully performed using moving shot technique. Black arrows indicate electrode. **D.** Six months after radiofrequency ablation, nodule volume (white arrows) was significantly reduced by 98.5%, and patient's residual symptoms had improved.

1.2 (65). Therefore, concomitant ethanol injection during RFA can effectively control active bleeding that occurs when internal fluid is aspirated, as well as reduce the number of sessions of RFA (Fig. 2).

Safety of Combined Ablation Techniques

Both EA and RFA are safe methods for treating benign thyroid nodules. Mild transient complications reported after EA include neck pain, hoarseness due to mild damage to the recurrent laryngeal nerve, and thyrotoxicosis (34, 36, 41, 66). Rare but serious complications of EA include leakage of ethanol, which induces perithyroid fibrosis and necrosis of adjacent structures (e.g., larynx and skin) (67, 68). However, the incidence of major complications is very low when EA is performed by experienced operators, with attention given to meticulous, US-guided handling of the needle. Moreover, leakage of ethanol during treatment of a cystic or predominantly cystic thyroid nodule can be prevented by limiting the maximum volume of ethanol injected to less than 50% of the volume of aspirated fluid, as well as by aspirating the ethanol after instillation.

Postoperative complications of RFA include pain, hoarseness, hematoma, skin burn at the puncture site, thyrotoxicosis, hypothyroidism, edema, and fever (49). A multicenter study reported an overall complication rate of 3.3% and a major complication rate of 1.4%, including voice change, nodule rupture, hypothyroidism, and brachial plexus injury. Most patients recovered without sequelae, and there were no procedure-related deaths. Studies evaluating the efficacy of combined EA and RFA, whether stepwise or concomitant, have reported no procedure-related deaths or major complications. By contrast, pain and fever were more frequently observed in patients treated for hepatocellular carcinoma who underwent combined RFA and EA than in those who underwent RFA alone. There were no procedure-related deaths or major complications (56). These findings indicate that combined RFA and EA will be safe and effective in treating benign thyroid nodules without major complications.

Perspectives

Image-guided ablation techniques have become the first-line therapy for benign thyroid nodules, with EA regarded as the procedure of choice for cystic thyroid nodules and RFA for benign solid thyroid nodules. Although EA remains the first option for predominantly cystic thyroid nodules, the recurrence rate for these lesions suggests that concomitant EA and RFA or EA followed by RFA may be more effective, especially for nodules with a large solid component or increased vascularity. Additionally, EA followed by RFA may be feasible for treating residual unablated areas after one session of RFA, particularly if the operator is less experienced and the residual volume is < 5 mL with no vascularity.

CONCLUSION

This review has described current treatment of benign thyroid nodules with three possible combinations of RFA and EA, both stepwise and concomitant. The indications for each method, as well as their clinical efficacy and safety, have been discussed. Since few studies have focused specifically on evaluating combined EA and RFA, future research should validate the efficacy of these techniques and further elucidate indications for their use.

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