



Ablation therapies for thyroid nodules and parathyroid adenomas: What we should know?

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Abstract

Thyroid nodules and parathyroid adenomas are common endocrine disorders that can lead to significant clinical symptoms and necessitate intervention. Traditionally, surgical resection has been the primary treatment for symptomatic or malignant thyroid nodules and parathyroid adenomas. However, surgery carries risks such as hypothyroidism, nerve damage and postoperative complications and may not be suitable for patients, especially those with comorbidities. Recently, non-surgical, image-guided ablation therapies, including ethanol ablation (EA), radiofrequency ablation (RFA), and microwave ablation (MWA), have emerged as viable alternatives for managing benign symptomatic thyroid nodules and parathyroid adenomas. This review highlights the indications, techniques, and outcomes associated with these ablative therapies. While the use of thermal ablation in managing thyroid nodules is well-supported by various guidelines, its application in parathyroid adenomas remains exploratory. The safety and efficacy profiles of these minimally invasive treatments make them promising alternatives to surgery, especially for patients who are high-risk surgical candidates or prefer non-surgical options.

Key words: Thermal ablation; thyroid nodules; parathyroid adenomas; microwave ablation; radiofrequency ablation

Introduction

Thyroid nodules are frequently encountered, appearing in 19%-35% of thyroid ultrasonography (US) studies and 8%-65% of autopsy studies [1]. Despite a significant rise in the incidence of thyroid malignancies over recent decades, the mortality rates for clinically significant thyroid cancers have remained stable for the past 80 years [2]. Consequently, the management of thyroid nodules has become a subject of considerable debate, with guidelines evolving over time. The classification of nodules for specific treatment protocols involves clinical examination, biochemical tests, imaging studies, and cytologic evaluation.

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Traditionally, surgery has been the primary treatment for thyroid nodules with malignant or suspicious cytologic diagnoses or autonomic function. However, there are patients with benign thyroid nodules that may enlarge, causing local pressure symptoms, such as neck pain, choking sensation, dyspnea, or dysphagia. A recent multicenter observational study indicated that up to 15% of benign nodules grow rapidly and continuously, whereas others remain relatively unchanged in size [3]. Historically, surgical resection has been recommended for the treatment of symptomatic benign thyroid nodules. The American Thyroid Association (ATA) guidelines suggest that surgical resection (hemithyroidectomy or total thyroidectomy) when a benign solid or predominantly solid nodule increases in size (>4 cm in diameter) causes local compressive symptoms or raises clinical concerns [4]. Although surgery is generally safe, it carries risks including hypothyroidism, bleeding, infection, hoarseness due to recurrent or superior laryngeal nerve injury, and postoperative hypoparathyroidism. Additionally, surgery poses risks related to general anesthesia and may not be suitable for individuals with underlying medical conditions [5]. Surgery is also the standard treatment for parathyroid adenomas; however, it carries postoperative morbidity and mortality risks, particularly in elderly and chronically ill patients. Furthermore, some patients with symptomatic hyperparathyroidism or symptomatic non-functioning parathyroid cysts either refuse surgery or are unsuitable candidates [6,7].

Non-surgical, image-guided procedures such as ethanol ablation (EA) and thermal ablations have been proposed as less invasive alternatives for managing benign symptomatic thyroid nodules and, to a limited extent, malignant nodules and parathyroid adenomas.

Ethanol Ablation

Ethanol ablation is a commonly used nonsurgical treatment for benign thyroid nodules that are either purely cystic or predominantly cystic (with a cystic portion greater than 50%). In recent years, EA has also been used for the treatment of recurrent thyroid cancer. When dealing with the local recurrence of thyroid cancer, surgery is generally considered the first-line treatment if imaging techniques confirm the recurrence site. However, reoperation can be technically challenging if previous surgeries disrupt the normal tissue plane, leading to fibrosis and scarring in the recurrent cancer area. Surgical complications were also possible.

External radiotherapy (RT) may be considered for

locoregional recurrences that cannot be surgically resected, or in cases with extranodal extension or soft tissue involvement, especially in patients without distant metastases [8]. However, RT can increase morbidity due to potential complications. Therefore, alternative procedures, such as image-guided EA or thermal ablation, have been suggested for patients concerned about RT complications, those who refuse RT, those at risk of serious complications from surgery, or those at high risk for surgery [9,10].

Indications

Cystic or predominantly cystic benign nodules

Ethanol ablation (EA) is recommended for the treatment of benign recurrent pure cysts or predominantly cystic nodules that lead to compression symptoms or neck swelling. EA can achieve a volume reduction of 85-95% in purely cystic nodules and 60-90% in predominantly cystic nodules [11,12]. The results were satisfactory for nodules with less than 20% solid components [13]. The first-line treatment for symptomatic benign pure cysts and predominantly cystic nodules is simple aspiration, although it is associated with a high recurrence rate. Therefore, EA is a reasonable approach for treating patients with recurrent cystic fluid accumulation after aspiration.

A cytological result from simple aspiration can confirm that a pure cystic or predominantly cystic nodule is benign, although cytological results in pure cysts are often non-diagnostic even with repeated examinations. For predominantly cystic nodules with benign ultrasound findings, such as a spongiform appearance or intracyst comet artifacts, EA can be performed after at least one benign fine-needle aspiration (FNA) result. For other predominantly cystic nodules with a solid component, at least two benign FNA results are required before EA is performed. The recurrence rate of thyroid cysts has decreased to less than 20% after EA [12].

Hyperfunctioning thyroid nodules

Ethanol ablation is an alternative to surgery and radioiodine for the treatment of hyperfunctioning nodules [14-17]. It has been reported that nodule size decreases, and hyperthyroidism improves post-EA treatment. However, the therapeutic effect diminishes as nodule size increases [17]. EA is most effective for hyperfunctioning solitary thyroid nodules with a volume of less than 30 mL [14-17]. When ethanol is used for cystic nodules, it remains in the cystic cavity,

resulting in low complication rates. However, injecting ethanol into solid nodules can be challenging because of leakage, which leads to unwanted complications. Additionally, the uneven distribution of ethanol in the nodules necessitates more treatment sessions than thermal ablation for nodules of the same size. Therefore, the use of EA is limited to large solid nodules.

Recurrent thyroid carcinoma

Surgery is the primary treatment for locally recurrent thyroid carcinoma, followed by radioactive iodine and/or thyroid hormone therapy. Minimally invasive treatments, such as RFA or EA, can be alternatives if surgery poses significant difficulty or severe side effects. Percutaneous EA is less invasive than surgery that requires general anesthesia, and repeated procedures are easy and safe, minimizing the risk of complications. While studies on EA's efficacy of EA in treating recurrent thyroid carcinoma are limited, it shows lesser efficacy in the complete disappearance of recurrent nodules and has a relatively higher recurrence rate than RFA [18]. Thus, EA may be recommended for complete ablation in patients with up to three locally recurrent nodules without distant metastases, or for palliative purposes in patients with known distant metastases and growing recurrent tumors.

Symptomatic parathyroid cysts

Simple aspiration was initially used to diagnose and treat symptomatic nonfunctioning parathyroid cysts, although recurrence was reported in 66.7% of cases, necessitating additional treatment. EA can be performed as a subsequent treatment modality for recurrent cases [6].

Standard procedure

It is essential to accurately characterize thyroid nodules and evaluate the surrounding critical anatomical structures using a pre-procedural US examination. The size, proportion, and vascularity of the solid component as well as the internal contents of the cystic component should be carefully assessed using US. Before proceeding, the patient received a thorough explanation of the procedure and provided informed consent, which included potential adverse events (such as pain or voice changes indicative of nerve damage from leakage).

The procedures are typically performed on an outpatient basis. The required materials include a 16-20 gauge needle, a 10-25 mL syringe, and 95-99% ethanol. While some variations exist depending on the operator, the

general method is as follows: the patient is positioned supine with slight neck extension. After sterilization of the skin, a local anesthetic (1-2% lidocaine) is injected into the puncture site. Depending on the viscosity of the cyst's contents, a single 16-20 gauge needle is inserted into the center of the cystic area under US guidance. A transisthmic approach is recommended to prevent needle movement and ethanol leakage when the patient swallows or speaks. Maximum aspiration is performed, and residual debris or colloids are removed via saline irrigation. The operator then slowly injects the appropriate amount of 95-99% ethanol into the cystic cavity, typically around 50% of the aspirated volume. Empirically, the total ethanol volume should not exceed 10 mL, even for large nodules, although more can be used if the ethanol will be removed post-procedure.

There is no definitive consensus regarding the total amount of ethanol required for injection. The exact amount should be based on the lesion size and internal content, the operator's judgment during the procedure, and patient compliance. Kim et al. [19] found a 2-minute ethanol retention time was sufficient due to the rapid cellular reaction of ethanol. However, there is no agreement on whether ethanol should be reaspirated after the procedure. Some studies suggest short ethanol retention times (at least 2 min) and complete removal to minimize patient discomfort and complications from potential ethanol leakage. Kim et al. [20] reported no difference in complications or success between groups in which ethanol was or was not aspirated after injection. Therefore, the choice of ethanol injection, with or without aspiration, depends on the operator's preference.

If the patient experienced pain during the injection, the operator should stop and check for perithyroidal leakage. Proper needle placement in the center of the lesion and avoiding excessive ethanol injection reduce the risk of leakage. If excessive ethanol is used, reaspirating can help alleviate pain. Upon completion of the procedure, the needle was swiftly withdrawn and light compression was applied to the puncture site for 5-10 minutes.

Complications

Ethanol ablation is a safe treatment option for cystic thyroid nodules, with most complications being mild and transient when performed by someone experienced in US-guided procedures. The most common complication is localized pain at the puncture site, but other potential issues include hematoma, facial flushing, feeling of intoxication, hoarseness, dyspnea, and transient

hyperthyroidism. Most patients experience mild pain immediately after the procedure, which can last a few minutes to several hours. This pain often resolves on its own and can be managed with analgesics. Hematoma, a common complication that can cause pain, can be prevented by applying compression to the puncture site for 10 minutes after the procedure.

Radiofrequency and microwave ablation

Radiofrequency ablation (RFA) generates heat through an electric current passing through a focal impedance circuit, causing cell death in the target tissues. Initially used for chronic neurogenic pain, RFA has been expanded to treat conditions such as cardiac ablation, renal sympathetic denervation, and varicose veins.

Heat generation via an electric current, known as the Joule effect, occurs because of frictional forces at the ionic level. Tissue impedance increases with a higher current magnitude and longer duration of flow, leading to coagulation necrosis, and irreversible cell damage starts at temperatures above 46°C for one hour, although this varies by tissue type [21]. Temperatures exceeding 100°C can cause tissue to boil, vaporize and carbonize, limiting heat conduction [22]. RFA for thyroid nodules typically employs 18-gauge needles measuring 7-10 cm with a 5-15 mm active tip, creating a cylindrical ablation zone approximately 2 cm in diameter.

Microwave ablation (MWA) is promising but lacks robust evidence. Studies have reported volume

reductions of 74.6%-90.0% after one year, with MWA potentially carrying higher complication risks due to less energy control and larger applicator diameters than RFA [23,24]. Despite advantages such as greater energy output, larger ablation fields, and shorter treatment times, MWA's broader tumor inactivation and efficacy of MWA in larger nodules are notable. However, meta-analyses, such as that by Qian et al., showed no significant difference in volume reduction between MWA and RFA six months post-operation, with MWA associated with higher major complication rates compared to RFA [25].

Indications

Thermal ablation, including techniques such as RFA, has been addressed by various national and international guidelines for managing both benign and malignant thyroid nodules. While the ATA briefly mentions thermal ablation in its 2015 guidelines, more specific recommendations come from organizations such as the Korean Society of Thyroid Radiology (KSThR), European Thyroid Association (ETA), and European Society of Cardiovascular and Interventional Radiology (CIRSE) (26-29).

For benign symptomatic thyroid nodules, all referenced guidelines suggest considering RFA when the nodules cause compression symptoms or cosmetic concerns. Symptoms such as dysphagia, dyspnea, neck pressure, foreign-body sensation, pain, and cough indicate a potential need for treatment. The KSThR emphasizes that while nodule size matters, location is critical;

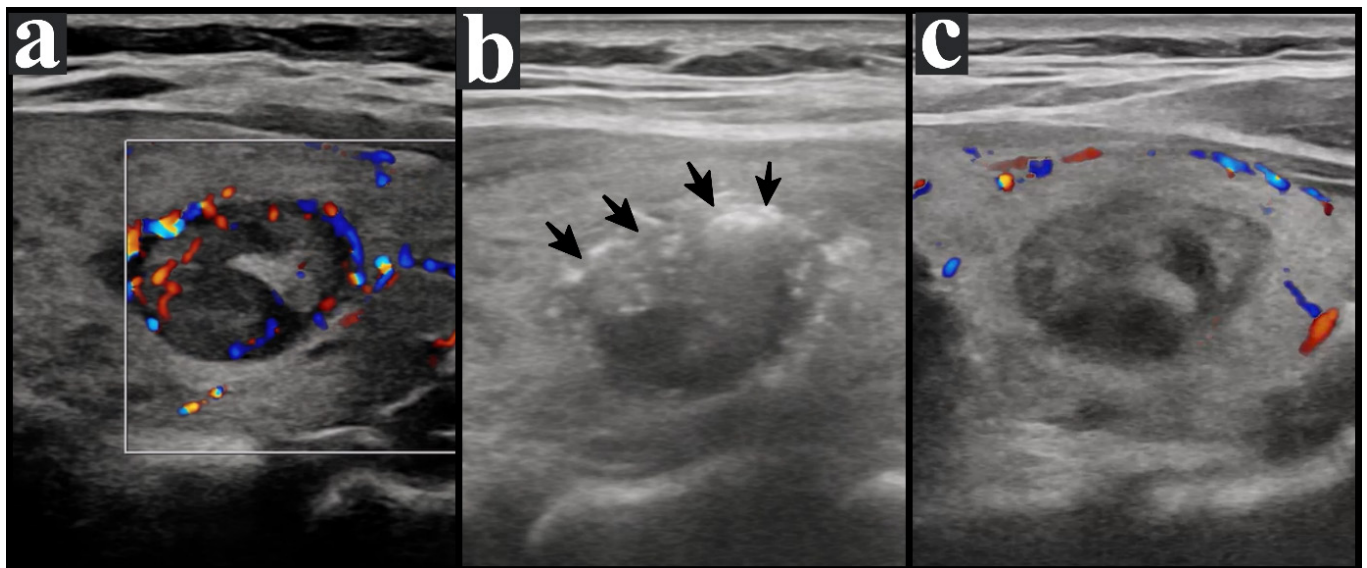


Figure 1. A 48-year-old woman with intrathyroidal parathyroid adenoma in the left thyroid lobe was confirmed by scintigraphy and fine-needle aspiration parathyroid hormone washout test. Figure A shows the internal vascularization of the parathyroid adenoma on preprocedural Doppler ultrasonography. Figure B shows immediate changes, such as echogenic gas bubbles (arrows), and Figure C shows the absence of internal vascularization of the parathyroid adenoma on postprocedure Doppler ultrasonography.

nodules in the isthmus can cause symptoms or cosmetic issues, even if they are smaller than 2 cm [26].

Regarding hyperfunctioning thyroid nodules, the guidelines generally recommend RFA in specific circumstances where surgery or radioactive iodine (RAI) poses risks, such as in patients at risk of prolonged hypothyroidism post-RAI or surgery. Guidelines from the KSThR and CIRSE caution against treating larger or multifocal autonomous nodules with RFA, suggesting RFA as an adjunct in younger patients.

For malignant nodules, the guidelines are less standardized owing to the limited evidence. Thermal ablation may be considered an alternative in patients who refuse or cannot tolerate surgery or in palliative care scenarios for advanced malignancies, as suggested by the KSThR guidelines [26]. ETA and CIRSE recommend minimally invasive techniques based on patient demographics, tumor characteristics, and local technical capabilities [28].

RFA is considered an alternative treatment for recurrent thyroid malignancies when surgery or RAI is contraindicated owing to factors such as previous surgeries or poor general health. This approach is supported by the ATA, ETA, CIRSE, and KSThR guidelines for high-risk surgical patients and those who refuse surgery.

Regarding parathyroid adenomas, while minimally invasive thermal therapies have been proposed as alternatives to surgery (**figure1**), there are currently no guideline recommendations or sufficient data on their efficacy and safety (30).

Standard technique

Thermal ablation procedures, whether using RFA or MWA, are typically conducted as outpatient visits or short hospital stays. These procedures are performed by specialized interventional radiologists skilled in thermal ablation techniques. A detailed overview of the process is as follows.

Thermal ablation involves positioning the patient in a supine position, with the neck extended for optimal access. Sedation levels vary, with local anesthesia often recommended by the KSThR, supplemented by liberal lidocaine injections into the thyroid capsule and nearby subcutaneous tissues, to minimize discomfort [26].

The equipment used includes 18-gauge electrodes for RFA, ranging from 7 to 10 cm with active tips of 5 to 15 mm, selected based on nodule size. MWA utilizes 16-18 G probes tailored to the specific characteristics of the target nodule. Confirmation of the target lesion is done via US, followed by an in-plane oblique approach to enter the thyroid gland and reach the nodule. This

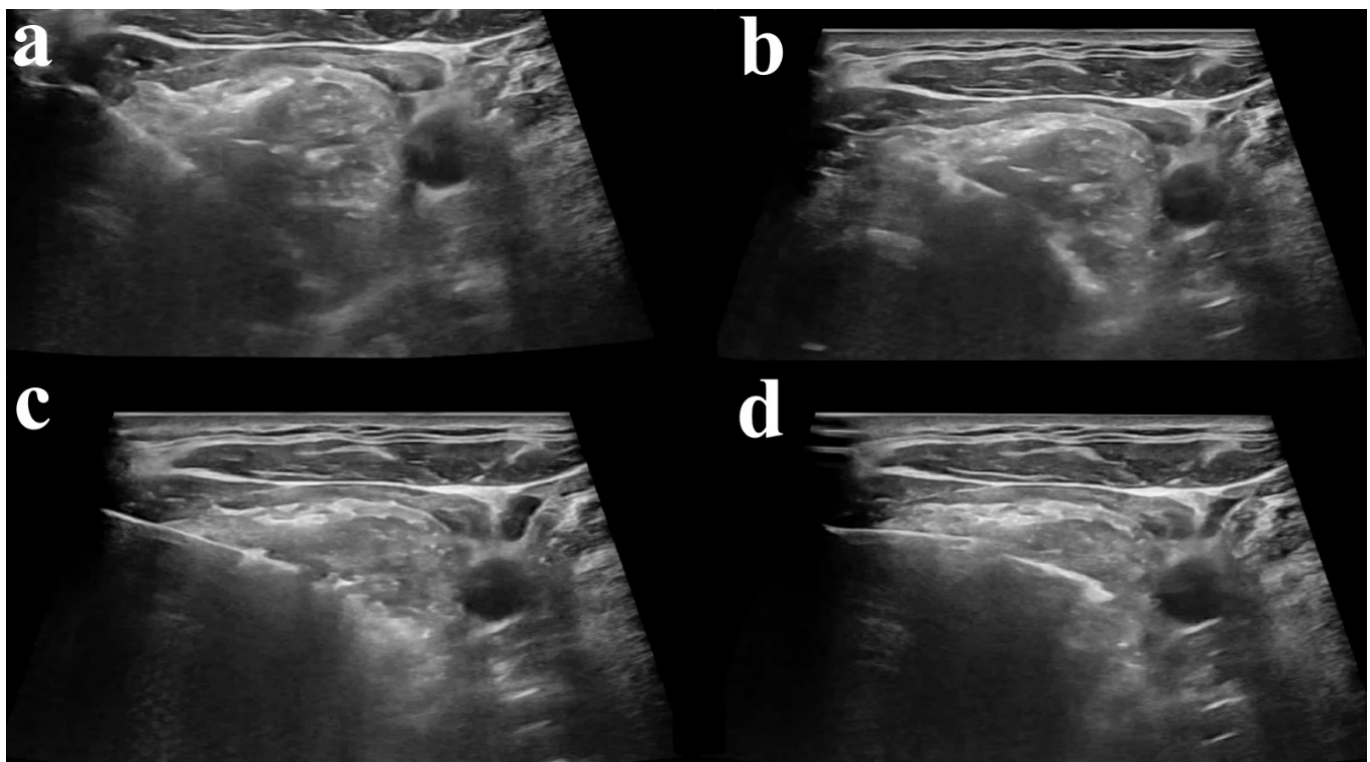


Figure 2. Moving shot technique. The electrode is left in the area until it is surrounded by a transient hyperechoic zone, which is then moved along the nodule from deep to the surface to the next subunit (a-d), and the procedure is repeated until the entire nodule is ablated.

approach ensures real-time confirmation of electrode placement and minimizes the risk of skin burns by increasing the distance between the active tip and skin surface. A transisthmic approach is often preferred to maintain electrode stability and prevent fluid leakage into the surrounding tissues, especially for nodules in the middle and lower thyroid regions.

The moving-shot technique is commonly employed during this procedure. This technique involves keeping the electrode in place until it is surrounded by a transient hyperechoic zone and then moving to the next position before the impedance rises sharply (**figure 2**). This ensures thorough nodule ablation while minimizing damage to the adjacent tissues. Care is taken to avoid ablating the outermost layer of benign nodules to prevent harm to nearby structures. In cases of malignancy, efforts are made to ablate the entire nodule.

Power settings typically range from 20 to 50 W and are adjusted based on the sonographic changes observed during the procedure. Continuous US monitoring of the electrode tip ensures effective ablation and prevents complications. Hydrodissection with a 5% dextrose solution is used when nodules are near critical structures, such as the skin surface, cervical muscle groups, carotid artery, or recurrent laryngeal nerve (danger triangle). This technique creates a barrier against thermal energy and minimizes the risk of injury to the adjacent structures (**figure 3**). Immediate sonographic changes, such as echogenic gas bubbles and increased impedance, confirm the effectiveness of ablation [26]. Postprocedural follow-up includes serial US examinations at 1, 6, and 12 months to assess nodule volume reduction and monitor any residual viable tissue.

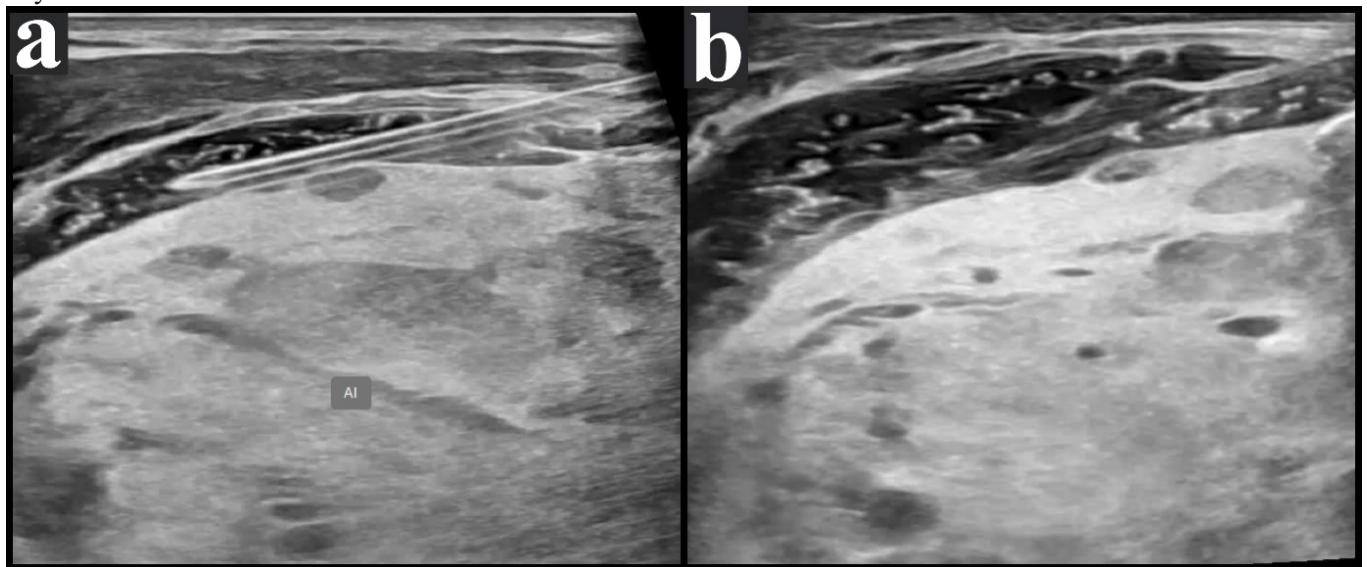


Figure 3. Hydrodissection. Placement of the fine needle outside the thyroid capsule (a) and injection of 5% glucose solution between the capsule and adjacent structures until successful hydrodissection is achieved (b).

Complications

Radiofrequency and microwave ablation are generally safe and well-tolerated procedures for the treatment of thyroid nodules. A meta-analysis of 24 studies and 2421 patients who underwent RFA revealed an overall complication rate of 2.4%, with major complications occurring in 1.4% of the cases [31]. In another study, MWA reported an overall complication rate of 11.5%, with major complications at 5.1% [32]. Both techniques showed comparable outcomes in terms of anesthesia and pain management.

Voice change is the most frequent major complication associated with RFA, occurring in approximately 1.5% of cases, with permanent changes observed in 0.2% of the patients [31]. This complication is attributed to direct thermal injury or laryngeal nerve irritation due to swelling or hematomas. Techniques such as hydrodissection, the moving-shot technique, and the trans-isthmic approach have proven effective in mitigating these risks [26].

Nodule rupture is another major complication of RFA, although rare, occurring in only 0.2% of the cases [31]. It typically results from acute swelling of the nodule due to edema or hemorrhage, leading to capsule rupture and spillage of the nodule contents into the surrounding tissues. Management usually involves conservative measures [33].

Conclusion

Minimally invasive ablative treatments, such as thermal ablation, offer effective and safe alternatives to surgery for the management of both thyroid nodules and parathyroid adenomas. Thermal ablation is particularly effective in

treating benign thyroid nodules, including toxic nodules. There is also a growing interest in its potential application in small primary papillary thyroid cancers, supported by promising outcomes from recent studies. Ethanol ablation and thermal ablation represent significant advancements in providing a more personalized approach to patient care. By carefully selecting suitable candidates, these treatments can achieve therapeutic responses in thyroid nodules and parathyroid adenomas while minimizing the complications and risks associated with surgical interventions.

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Declaration competing interest

The authors declare that they have no competing of interest.

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