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Radiofrequency Ablation Therapy for Benign Thyroid Nodules: A Literature Review

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Abbreviations:
RFA: Radiofrequency ablation;
AFTN: Autonomously functioning thyroid nodules;
PEA: Percutaneous ethanol therapy ablation
VRR: Volume reduction rate;
MWA: Microwave ablation.

ABSTRACT

Background: Benign thyroid nodules are the most common thyroid disorders in the world. Ninety percent of thyroid nodule cases found in the hospital are benign nodules. In the case of benign thyroid nodules, it is difficult to determine the appropriate balance between the risks and benefits of surgical therapy as a curative approach, whereas an approach with suppressive therapy reports unsatisfactory results and requires a long treatment time. Another alternative therapy for benign thyroid nodules is radiofrequency ablation (RFA) therapy, which is used for benign thyroid nodules with clear and solitary nodule margins. Although several studies have shown that RFA is a safe technique, there are some associated complications, which are minor. Therefore, reviewing the literatures is critical to evaluate the effectiveness of RFA in reducing the size of benign thyroid nodules and the complications that occur.
Methods: This study aims to conduct a literature review on RFA therapy for benign thyroid nodules. Literature searching was conducted on PubMed, Scopus, and ScienceDirect.
Result: Based on a review of 27 literature, RFA can effectively reduce the size of benign thyroid nodules by up to 80% within 6 – 12 months of initial therapy. After the RFA procedure, it was reported that 83% of patients had no complications and 16.1% of patients experienced mild-moderate complications that were reversible.
Conclusion: RFA can effectively reduce the size of benign thyroid nodules, and RFA has a good safety profile in treating benign thyroid nodules.
Key words: radiofrequency ablation, thyroid benign nodule

INTRODUCTION

Thyroid benign nodules are the most common thyroid disorders in the world. Ninety percent of cases of thyroid nodules found in hospitals are benign nodules (1,2). Benign thyroid nodules occur due to several acquired diseases such as Hashimoto disease, follicular adenoma, and subacute thyroid infection. Women and the elderly are at higher risk for thyroid nodule diseases. Other risk factors include any history of iodine deficiency and radiation exposure (1,3-5). The first-line therapy for benign thyroid nodules is either pharmacological therapy (thyroid hormone therapy) or surgery (5,6).

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The treatment of benign thyroid nodules presents a challenge in determining the optimal approach that balances the associated risks and benefits. Although surgical therapy is curative, its appropriateness is difficult to determine. Conversely, suppressive therapy has been reported to produce unsatisfactory results and necessitates long treatment times. Therefore, the selection of an appropriate treatment strategy requires careful consideration of the available options, with the aim of achieving optimal outcomes while minimizing adverse effects.

Another alternative therapy for benign thyroid nodules is radiofrequency ablation therapy (RFA), which is used for benign thyroid nodules with clear and solitary nodule margins (7,8). RFA is performed using local anaesthesia and an electric current of 200 kHz -1200 kHz (7,8). RFA works by concentrating the heat generated by an electric current through the electrode to the nearest thyroid nodule tissue, resulting in thyroid nodule tissue necrosis or development of fibroblastic tissue, ultimately reducing the size of the nodule.

Indications for RFA include the symptoms of compression of the nodule to the surrounding tissue, aesthetic effects, and in cases of autonomously functioning thyroid nodules (AFTN) (9). In the event that percutaneous ethanol therapy ablation (PEA) is unsuccessful, thyroid nodules may be classified as solid nodules, predominately solid nodules, or predominantly cystic nodules. Currently, neither the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom nor a professional association from Austria have made any recommendations regarding nodule size. However, an Italian association recommends RFA for large nodules (volume > 20 mL), especially those with local symptoms or aesthetic problems (10). Patients with thyroid nodules with a maximum diameter of more than 2 cm who continue to grow can be considered for RFA (11). RFA as a therapy for thyroid nodules has several advantages, including unnecessity for general anaesthesia, shorter treatment time, minimal scarring, and good results (12). In a study conducted by Cesereo et al., it was found that 50–80% of patients who underwent RFA therapy reported significant results in volume reduction compared to patients who did not undergo surgery (9). Although the success rate related to nodule size reduction is relatively good, some studies with a more extended period have demonstrated a trend toward increasing thyroid nodule size two to three years after RFA therapy (7-9,13). Despite several studies have shown that RFA is a safe technique, there are some associated complications, some of which are minor. The most common minor complications include pain, transient voice changes, sunburn, hematoma, and transient thyroiditis may occur but are less common (14).

Therefore, a literature review is critical to evaluate the effectiveness of RFA in reducing the size of benign thyroid nodules and the associated complications.

MATERIAL AND METHODS

The study was designed to provide a comprehensive literature review of the use of radiofrequency ablation (RFA) therapy for the treatment of benign thyroid nodules. The research was conducted by searching the literatures through online databases such as PubMed, Scopus, and ScienceDirect using the keywords "radiofrequency ablation"[MeSH Terms] AND ("thyroid nodule" [MeSH Terms] OR "thyroid nodes" [Title/Abstract]) AND ("diameter reduction"[Title/Abstract] OR "size reduction"[Title/Abstract] OR "volume reduction"[Title/Abstract] OR "complications" [Title/Abstract]). The selection of studies was based on their relevance to the research topic, which was determined by evaluating the title, abstract, or full text of each study.

Inclusion criteria

- Studies are randomized or cohort clinical trials.
- Adult patient with benign thyroid nodule.
- Studies on the use of RFA therapy in benign thyroid nodules, either as additional therapy, main therapy, or a comparison between RFA and thyroidectomy.
- The output that is seen is the effectiveness of RFA therapy, which is assessed from the reduction in the nodule size and complications after RFA therapy is carried out.
- English language.
- Last five year study.

Exclusion criteria

- The study is a conference, abstract, poster, and commentary.
- Not available in full script.
- Test in vitro, ex vitro, in vivo, and ex vivo.

RESULTS

Literature searches were conducted in various online databases such as PubMed, Scopus, and ScienceDirect, and the screening process was carried out until July 2022. As this paper is a literature review, a qualitative synthesis was performed, and no quantitative analysis was conducted. Ultimately, 27 studies meeting the criteria were included in this study. The literature search flow is shown in *fig. 1*.

The characteristics of each literature are presented in Appendix 1, whereas the results are shown in *table 1*.

DISCUSSION

Thyroid nodules are one of the most common lesions in daily surgical practice and 50% can be detected by ultrasound examination and demonstrable by cytological examination. In the management of benign thyroid nodules, those exceeding a size of 2 cm or exhibiting non-responsiveness to suppressive therapy necessitate further attention. RFA is a non-invasive treatment that has been proven to be effective and safe in benign thyroid nodules.

All of the studies found in the last five years used both trans-isthmic and moving-shot techniques. It is hypothesized that the moving-shot technique is more flexible than the fixed-needle technique and the size of the ablation unit can be adjusted by changing the speed of movement of the electrode tip of the RFA (15). This technique, coupled with the trans-isthmic technique also protects vital structures around the nodule by using the ablation unit, which is relatively smaller and may prolong the action time at the centre of the nodule.

Overview of Radiofrequency Ablation

RFA is a treatment modality that is used for benign thyroid nodules causing cosmetic or symptomatic issues. The procedure utilizes high-frequency alternating electric current oscillating between 200 and 1200 kHz generated by an electrode that is applied to the nodule. The current induces rapid movement of ions and generates frictional heat, thereby causing coagulative necrosis and irreversible damage to the surrounding tissue near the electrode at temperatures ranging from 50°C to 100°C. Temperatures higher than 100°C can cause vaporization and carbonization, leading to an increase in tissue impedance, which interrupts the transfer of electric current and heat energy. The conduction of heat also causes further damage to the surrounding tissue (7). Care is taken to avoid injury to nearby structures, particularly within the "danger triangle" where the recurrent laryngeal nerve is tethered to the trachea close to the posterior-medial aspect of the thyroid (14).

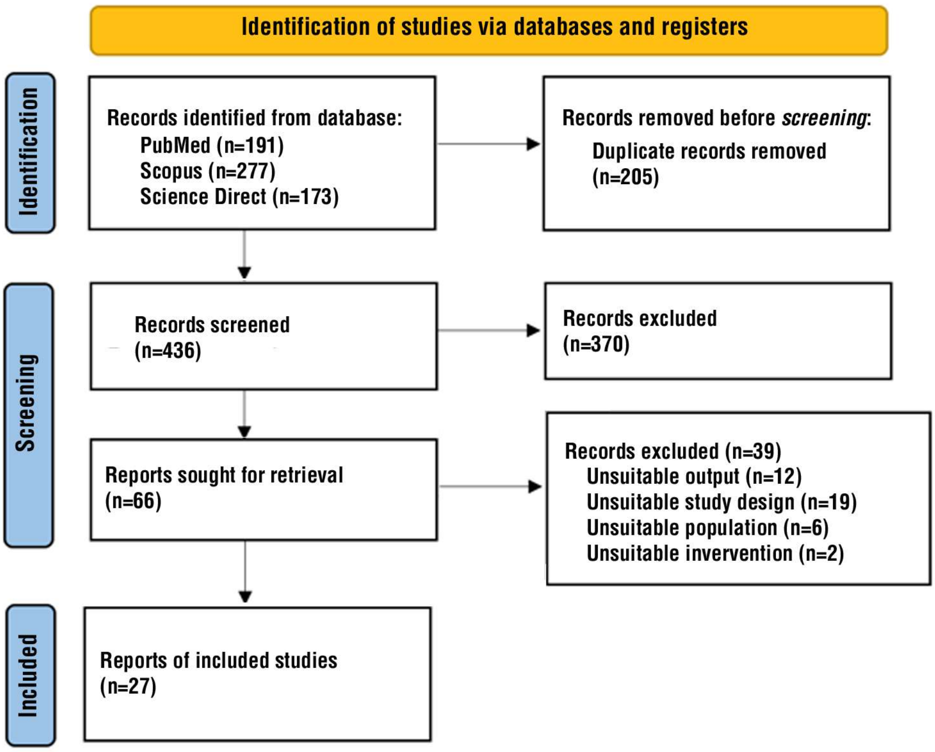

Figure 1 - Literature search following Prisma flow 2020

Table 1 - Results of screened literatures

Author, year	Number of subjects	Nodul type	Initial nodule volume (mL)	VRR (%)	Complication, n (%)	
					Minor	Major
Cesareo R, 2021 (16)	58	BNTN	26.5 ± 21.2	70.9 ± 16.9	Unknown	Unknown
Cesareo R, 2020 (17)	60	Unspecified	25.4 ± 22.3	64.3	Haematoma, 3 (5); local pain, 6 (10); headache, 1 (1.7)	Dysphonia, 1 (1.7); hyperparathyroidism, 1 (1.7)
Lee MK, 2023 (18)	287	Unspecified	6.4 ± 7.7	6 months: 75.2 ± 23.8 60 months: 91.9 ± 14.8	Haematoma, 11 (3.83); transient vocal cord paralysis, 3 (1.05); burn wound, 1 (0,35)	Permanent vocal chordcord paresis, 2 (0.69)
Lang BHH, 2022 (19)	174	Non-toxic nodule	Single RFA¶ group: 16.57 ± 17.01 Sequential RFA group: 13.23 ± 12.11	Single RFA group: 3 months: 67.39 ± 15.43 6 months: 77.29 ± 13.59 Sequential RFA group: 3 months: 63.89 ± 18.04 6 months: 73.38 ± 16.89	Single RFA group: Vocal cord paresis, 2 (2.4) Sequential RFA group: Vocal cord paresis, 2 (2.2)	Unknown
Escobedo, 2022 (20)	72	Non-toxic nodule	Median 23.50 (min. 2.5 – max. 81.0)	1 months: 34.2 ± 17.2 3 months: 50.8 ± 15.8 6 months: 60.3 ± 17.4 12 months: 58.87 ± 21.3 24 months: 70.85 ± 21.0	NA	Unknown
Vu D, 2022 (21)	17	Toxic nodule	13.07 ± 8.45	1 month: 42.77 3 months: 63.13 6 months: 78.3 24 months: 95.65	NA	Unknown
Jin H, 2021 (22)	289	Unspecified	Median 9.8 (min. 5.1 – 19.8)	1 month: 15.4 (min. 8.2 – max. 22.6) 3 months: 48.2 (min. 36.9 – max. 59.5) 6 months: 68.1 (min. 60.0 – max. 59.5) 12 months: 80.1 (min. 78.3 – max. 81.9) 18 months: 89.2 (min. 84.4 – 94.0)	Burn wound, 3 (1.03)	Unknown
Nguyen VB, 2021 (23)	78	Unspecified	6.11 ± 5.46	1 month: 41.47 ± 19.92 3 months: 64.72 ± 17.71	Transient voice changes, 2 (2.56)	Unknown
El-Galil MSA, 2021 (24)	40	Unspecified	Median 15 (Q1 8.5 – Q3 39.5)	1 month: 58.41 ± 15.27 3 months: 73.26 ± 11.22 6 months: 82.54 ± 12.49	Transient voice changes, 2 (2.5); haematoma, 2 (2.5); burn wound, 2 (2.5)	Unknown
Deandrea M, 2019 (25)	337	Solid nodule	Median 20.7 (95%IK 13.7 – 33.1)	6 months: 64.7 12 months:71	Oedema, 20 (5.93); Haematoma, 32 (9.50); transient voice changes (2.97)	Infected nodule, 1 (2.97)
Cappelli C, 2019 (26)	43	Toxic (17) Non-toxic (26)	Functional nodule: 7.2 ± 5.0 Non-functional nodule: 10.6 ± 7.0	69.1 ± 17.3	Haematoma, 1 (2.33)	Unknown

Table 1 - Cont'd

Author, year	Number of subjects	Nodul type	Initial nodule volume (mL)	VRR (%)	Complication, n (%) Minor	Major
Jung SL, 2018 (27)	345	Unspecified	14.2 ± 13.2	80.3 ± 13.7	Haematoma, 10 (3.6); first- degree burn wound, (0.4)	Transient vocal changes, 2 (0.7); hyperthyroidism, 1 (0.4)
Dobnig H, 2018 (28)	277	Unspecified	32.6 ± 20.9	3 months: 68 ± 16 12 months: 82 ± 13	Pain, 28 (10.11); intramuscular haematoma, 4 (1.4); hypotension, 2 (0.7); subcutaneous haematoma, 12 (4.3); headache, 1 (0.3); dysphagia, 9 (3.2); cervical stiffness, 4 (1.4); fever, 4 (1.4); cervical oedema, 1 (0.3); reversibel hyperthyroid, 2 (0.7).	Hypothyroidism, 1 (0.3); infected wound needing surgery, 1 (0.3)); transient vocal changes, 5 (1.8)
Cheng, 2017 (29)	649	Unspecified	7.22 ± 6.76	3 months: 67.6 ± 20.33 6 months: 84.1 ± 13.5 12 months: 89.6 ± 20.0	Haematoma, 13 (2)	Vocal changes, 29 (4.47); nodule ruptured, 2 (0.31)
Kim HJ, 2022 (30)	88	Unspecified	14.3 ± 16.2	84.6 ± 19.0	NA	NA
Li Y, 2022 (31)	52	CBTN	5.83 ± 19.17	6 months: 49.54 ± 52.51 12 months: 73.63 ± 35.55 24 months: 84.53 ± 25.98	Cervical pain, 1 (1.92); local swelling, 1 (1.92); electrode fracture, 1 (1.92)	Unknown
Lin W-C, 2022 (32)	762	Unspecified	21.51 ± 27.13	1 month: 37.76 ± 48.80 3 months: 59.29 ± 25.65 6 months: 73.24 ± 23.19	Burn wound, 1 (0.1); transient hyperthyroidism, 2 (0.2); haematoma, 4 (0.4)	Vocal changes, 22 (2.6); ruptured nodule, 9 (1); ptosis, 2 (0.2)
Lin Y, 2022 (33)	24 (11 single RFA : 13 sequential RFA)	Unspecified	Single RFA : 43.2 ± 19.3 Sequential RFA: 48.9 ± 44.4	Single RFA: 1 months: 78.6 ± 18.7 6 months: 93.9 ± 9.9 Sequential RFA: 1 months: 67.4 ± 17.8 6 months: 94.8 ± 3.8	Single RFA: Vocal changes, 2 (8.33) Sequential RFA: Pain, 1 (4.1)	Single RFA: Massive haemorrhage, 1 (4.1) Sequential RFA: Massive haemorrhage, 1 (4.1); extrathyroidal haematoma, 1 (4.1)
Chen MH, 2022 (34)	135	Unspecified	28.44 ± 37.97	1 month: 32.65 ± 43.31 3 months: 58.66 ± 23.41 6 months: 70.61 ± 17.85 12 months: 79.21 ± 15.96 24 months: 85.53 ± 13.29	Not mentioned, 8 (5.92)	Unknown
Ho T-L, 2022 (35)	18	Unspecified	20.0 (1.39–59.8)	1 month: 39.6 ± 23.4 6 months: 60.02 ± 18.40 12 months: 70.18 ± 22.68	Unknown	Pseudocyst formation, 1 (5.6); Horner syndrome, 1 (5.6); Thyroiditis, 1 (5.6)
Li J, 2021 (15)	1289	Solid nodule (262) Solid-cyst nodule (1027)	Solid nodule: 5.60 ± 4.52 Solid-cyst nodule: 8.12 ± 6.32	Solid nodule 3 months: 56.61 ± 19.50 6 months: 65.81 ± 20.24 12 months: 73.81 ± 18.94 Solid-cyst nodule 3 months: 66.58 ± 23.16 6 months: 77.65 ± 18.70 12 months: 82.71 ± 16.90	NA	NA

Table 1 - Cont'd

Author, year	Number of subjects	Nodul type	Initial nodule volume (mL)	VRR (%)	Complication, n (%)	
					Minor	Major
Hussain I, 2021 (36)	42	Toxic (18) Non-Toxic (22)	Median 8 (min. 0.4-max. 54.95)	70.8 (min. 31.7 – max. 96.3)	Haematoma, 1 (2.38); hoarseness, 1 (2.38)	Unknown
Yan L, 2021 (37)	20	Unspecified	15.04 ± 21.17	3 months: 62.81 ± 21.56 6 months: 74.83 ± 13.44 12 months: 81.65 ± 13.59 24 months: 85.42 ± 12.16	Pain, 8 (40)	Unknown
Lin WC, 2020 (38)	136	Unspecified	31.9 ± 39.1	1 month: 40.4 ± 3.3 3 months: 61.7 ± 19.9 6 months: 72.2 ± 17.3	Vocal paralysis, 5 (3.68); burn wound, 1 (0.74); haematoma, 1 (0.74)	Ruptured nodule 1, (0.74)
Guang Y, 2019 (39)	103	Unspecified	21.2 ± 19.7	1 month: 53.1 ± 15.7 3 months: 65.9 ± 13.1 6 months: 71.4 ± 12.6 12 months: 78.6 ± 11.5 24 months: 87.5 ± 4.6 In population with intermediate nodule sizes (13.1 – 30 ml), n = 43	Localized pain, 12 (11.6)	Unknown
Rabuffi P, 2019 (40)	77	Solid nodule	17.9 ± 15.6	6 months: 64.1 ± 20.0 12 months: 70.95 ± 20.8	Localized pain, 6 (7.8)	Unknown
Vuong NL, 2019 (41)	184	Unspecified	Median 6,18 (Min. 0.60 – max. 96.27)	1 month: 45,5 3 months: 66,8 6 months: 74,3 12 months: 81,0	Transient vocal changes, 2 (1.1)	Unknown

¶RFA, Radiofrequency Ablation
NA Result are not listed in the research manuscript

RFA is indicated for patients with benign thyroid nodules with symptoms or cosmetic issues. In benign thyroid nodules, the use of RFA successfully improves thyroid functional status. Some studies also found a reduction in the need for antithyroid medication, which even could be stopped in 23 to 89% patients. RFA is also effective for toxic or pre-toxic autonomously functioning thyroid nodules (AFTN). RFA can also be performed for curative or palliative purposes in recurrent thyroid cancers at the thyroidectomy bed and cervical lymph nodes for patients at high surgical risk or those who refuse surgery. While surgery is the standard treatment for primary thyroid cancer, RFA can be considered as an alternative for patients who refuse surgery or are unable to undergo it. However, RFA is contraindicated for pregnant patients and patients with cardiac pacemakers. Furthermore, the location of the nodule, which is close to critical structures such as the nerve to the vocal cord, major blood vessels, or esophagus, is also a relative contraindication (42).

Based on the guidelines recommended by The Task Force Committee of the Korean Society of Thyroid Radiology, RFA is a safe procedure, well-tolerated by patients, and associated with only a low incidence of complications (42). A meta-analysis found that the overall complication rate for benign nodules was 2.11% (95% confidence interval [CI], 1.15% to 3.06%), while the major complication rate was 1.27% (95% CI, 0.81% to 1.73%). In the case of recurrent thyroid cancers, the overall complication rate was higher, at 10.98% (95% CI, 4.82% to 17.15%), with a major complication rate of 6.71% (95% CI, 3.05% to 10.36%) (43). Other complications have also been reported, including major ones such as nerve injuries, nodule rupture, and permanent hypothyroidism, as well as minor complications such as hematoma, vomiting, lidocaine toxicity, transient thyrotoxicosis, skin burn, hypertension, and pain.

There are no life-threatening complications were reported, with only 0.21% sequelae rate (44).

Effectiveness of RFA on the size of benign thyroid nodules

According to all reviewed studies, RFA can effectively reduce the size of benign thyroid nodules by up to 80% within 6 – 12 months of initial therapy. It is possible to achieve results through RFA monotherapy. RFA single therapy reported similar effectiveness as sequential therapy. Lang et al., (2021) reported that ablation of benign thyroid nodules in two or more sessions showed similar results to a single RFA, regardless of the initial size of the thyroid nodule (19). This study found that the most important factor affecting the volume reduction rate (VRR) is the amount of RFA energy administered per nodule volume, with a p-value of 0.041 (19). Compared with laser ablation, RFA was proven to be more effective than laser ablation. Studies by Cesareo et al. (16,17) reported that RFA had a higher success threshold than laser ablation based on the ability of RFA to improve VRR. The exact cause of the higher effectiveness of the RFA compared to laser ablation is not yet to be known. It may be suggested that the energy released by RFA, which tends to be higher, is related to this effectiveness. According to Deandrea et al., more than 2670 J/mL of energy per volume is required for successful non-toxic thyroid nodule ablation (25). However, in the study conducted by Cesareo et al, the mean energy per volume of nodules delivered by RFA was 2012.6 ± 96.5 J/mL and the reported results do not differ from the study of Deandrea et al. (16). The energy delivered by laser ablation is at least 400 J/mL and cannot be too high due to the laser ablation being in direct contact with the nodule tissue, which releases heat right from the end. This increases the risk of carbonization of the surrounding tissue and reduces heat conduction to the surrounding tissue of the nodule.

Compared with microwave ablation (MWA), RFA also has the same effectiveness as MWA. Similar to laser ablation, MWA is also a thermal ablation technique. The study by Jin et al. (2021) reported that at the 18th month of follow-up, both MWA and RFA groups had a similar VRR with MWA at 91.7% and RFA at 89.2% (p-value = 0.58) (22). The quality of life score between the two groups was also reported to not have a significant difference (22). In contrast, when comparing RFA therapy and thyroidectomy, a significant difference was observed in quality of life in the RFA group, due to faster healing and better cosmetic results in the RFA group. This study has a small sample size and relatively short follow-up time.

A prospective study in 2017 by Cheng et al. involving 1252 patients divided into two groups, namely RFA and MWA therapy, reported that the VRR and maximal diameter reduction ratio (MDRR) in the group of patients with RFA were significantly better compared with the group of MWA patients after six months of follow-up (29). This study reported that these differences are based on the basic principles of RFA and MWA. The temperature produced by MWA is more than 150°C, not different from the central temperature of the nodule tissue so that carbonization of the ablated lesion can easily form, even with only low power by MWA (30 – 50 Watts). This is in contrast to the central temperature produced by RFA which does not exceed 110°C, and the incidence of carbonization in lesions by RFA is rarely found (29).

Complications of the RFA procedure

Radiofrequency ablation (RFA) is generally considered to have a favorable safety profile. A review of studies has shown a rate of major complications of 5.6%, which corresponds to one in fifteen cases, based on data from a small retrospective study. This suggests that RFA is a reasonably safe procedure that poses only a modest risk of major complications (35). Study by Ho et al reported a complication of pseudocyst formation, Horner syndrome, and thyroiditis. In this study, cases of thyroiditis appeared two weeks after ablation with symptoms of tachycardia. The patient was given carbimazole and the complaints improved. The incidence of thyroiditis has been reported to occur as a manifestation of the normal inflammatory process in response to the procedure. The occurrence of Horner's syndrome, in this case, could be caused by injury to the middle cervical sympathetic ganglion or compression by hematoma or oedema. The patient was managed conservatively and symptoms improved after 6 months (35).

The study by Dobnig et al. reported that 89.9% (249/277) of patients receiving RFA felt no pain at the time of the RFA procedure and 10.1% (28/277) of patients experienced moderate to severe pain (28). Based on these results, it is suggested that local anaesthesia in RFA alone is sufficient to provide analgesia, although, in some patients, additional sedation using midazolam or general anaesthesia may calm the anxious patient before the procedure. Meanwhile, after the RFA procedure, it was reported that 83% of patients had no complications and 16.1% of patients experienced mild-to-moderate complications that were reversible. In this study, it was reported that only 0.7% of patients had irreversible complications, namely hypothyroidism and wound infection (28).

CONCLUSION

RFA is a minimally invasive procedure that is effective for reducing the size of benign thyroid nodules and has minimal complications.

Authorship

All authors have made substantial contributions to all of the following: (1) conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

Conflicts of interest and funding

The authors of this study have stated that they have neither received any funding nor have any conflict of interest. The authors affirm neither conflict of interest nor funding source in this study.

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