Ultrasound-guided radiofrequency ablation versus total thyroidectomy for benign solitary thyroid nodules by fine-needle aspiration cytology

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Background
Nodular disorders of the thyroid gland are frequently detected in the general population; most of these nodules are benign. However, malignant cases have been increasing in the past decades. Ultrasound is the most common imaging modality used to assess thyroid nodular lesions, plan patient work-up and guide minimally invasive therapy.
Aim
The aim of this study was to evaluate the current status of radiofrequency ablation (RFA) treatment to evaluate the indications, techniques, complications, limitations, and outcome assessment in benign thyroid nodules in comparison with total conventional thyroidectomy.
Patients and methods
Twenty-four patients who underwent ultrasound-guided RFA were prospectively compared to 33 patients who underwent total thyroidectomy, between June 2017 and December 2018, and a 1-year follow-up at Ain-Shams University Hospitals. Efficacy, tolerability, and costs were compared. The contribution of the final pathology was also considered.
Results
There were significant differences in volume reduction in the size of the nodule after RFA during follow-up, with the initial volume of 12.41±1.63 ml decreasing to 3.61 ±0.5 ml after 12 months. Three (12.5%) patients showed progression in size after the 12th month. Pain, cosmetic appearance, and overall satisfaction were more acceptable in RFA than surgery. Compression symptoms and thyrotoxicosis disappeared rapidly and completely after surgery.
Conclusion
Surgical treatment for a solitary thyroid nodule remains the main line of treatment in view of missed malignancies by fine-needle aspiration cytology. Surgery is also more effective in abolishing thyrotoxicosis than RFA. However, for high-risk patients or those who refuse surgery, RFA is an effective alternative to surgery; it has the advantage of fewer complications and greater patient satisfaction.

Keywords:
benign thyroid nodule, radiofrequency ablation, solitary thyroid nodule, total thyroidectomy, ultrasonography

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Introduction

Thyroid nodules are frequent in the general population, with a prevalence of 20–67%; about 50% occur in the individuals older than 40 years of age, with a higher incidence in females [1,2]. Most thyroid nodules are hyperplastic [3]; however, a proportion (7–15%) is malignant. Thyroid nodules may become clinically significant and even serious in less than 1% of cases [4]. There has been a 2.5-fold elevation in thyroid malignancy in the last 30 years [5].

Studies had demonstrated that 6% of thyroid neoplasms diagnosed by ultrasound-guided fine-needle aspiration cytology (FNAC) as benign nodules may be diagnosed as malignant nodules by postoperative pathology [6]. Therefore, symptomatic benign and highly suspicious thyroid neoplasms should be actively treated [7,8]. Surgery, especially total thyroidectomy, can eliminate the symptoms of thyroid nodules and the risk for dysplastic changes. Despite being effective, surgical resection usually has some risks and drawbacks [9,10]; minimally invasive nonsurgical techniques are required in the management of thyroid neoplasms [11].

Radiofrequency ablation (RFA) has been used effectively in treating liver tumors [12]. Because of the advantages of safety, efficacy, and good cosmetic result, RFA has been used for the treatment of benign and malignant thyroid nodules that are not appropriate for surgery [13,14].

RFA cannot remove thyroid nodules immediately; it induces necrosis and involution of thyroid nodules, resulting in volume reduction and improvements in clinical symptoms, with the efficacy of RFA being similar to that of thyroid surgery [14].

The Korean Society of Thyroid Radiology recommendations listed the complications and side effects of RFA in the management of thyroid neoplasm hypothyroidism, like various degrees of pain, voice change, vagus nerve, and sympathetic ganglion damage. Complications were reported in 48 (3.3%) patients and major complications in 20 (1.4%) patients. They also reported that to avoid these complications, continuous and cautious ultrasound-guided tracing of the electrode tip is mandatory during the RFA [15].

The aim, of our study was to assess the efficacy and outcomes of RFA for the treatment of begin thyroid nodules in comparison with conventional total thyroidectomy.

Patients and methods

This study was carried out on 57 adult patients who presented to the surgery outpatient clinics in Ain-Shams University Hospitals from June 2017 to December 2018 with a 12-month follow-up period; they presented with symptomatic solitary thyroid nodule (STN) and were treated by either RFA (group A, n=24) or by total thyroidectomy (group B, n=33). Ethical approval was obtained from the Ain-Shams University ethical committee. In our hospital, surgery was primarily advised for patients and in case of patient refusal or if the patient had a poor general condition, RFA was offered as an alternative. Patients who underwent RFA were informed about the risks of possible dysplastic changes and malignant transformations.

Inclusion criteria

Adult patients who presented to the general surgery outpatient clinics with a solitary thyroid nodule (solid or partially solid) and showed benign criteria by ultrasonography (TI-RADS 2, 3) and Bethesda class I, II on FNAC were included. Patients agreed to continue the follow-up for 1 year.

Exclusion criteria

Patients who had undergone previous neck surgery were excluded. Patients with suspected ultrasonographic malignant criteria (TI-RADS 4, 5) and patients with suspected cytological atypia or dysplasia (Bethesda class III, IV, V, VI) were also excluded.

All patients underwent full clinical assessment, laboratory investigations (including thyroid-stimulating hormone, free triiodothyronine, free thyroxine, anti-thyroid peroxidase antibodies and thyroglobulin antibody serum levels) and ultrasound imaging by a senior radiologist using a 5–12 MHz linear transducer and a real-time ultrasound system. FNAC was performed for all the lesions before the interventions. A written informed consent was signed by each participant.

Radiofrequency ablation

Patients undergoing RFA were categorized as group A. Ablation (Figs 1 and 2) was performed by an interventional consultant radiologist (with 14 years' experience) using a radiofrequency generator (RF Medical, Seoul, Korea) and an 18 G internally cooled electrode (RFT electrode), 70 mm in length, 1 mm in diameter and exposure 7 mma 0.5-cm active tip (RF Medical). Lidocaine was used as a local anesthetic, and ablation was performed using a 2 mm safety margin from the deepest point of the nodule in a unit-by-unit method by moving the electrode.

Ablation was started by 10–15 W of power. A hypoechoic zone indicated effective ablation at the tip of the electrode within 10 s. In some cases, power was increased up to 40 W to achieve ablation. Real-time monitoring by ultrasound was performed to ensure the correct position of the needle during the procedure. All procedures were performed on an outpatient basis and patients were discharged after 2 h of observation.

Surgery

Total thyroidectomy (Fig. 3) was performed for all patients of group B by the same surgical team. Under general anesthesia, the patient was placed in a supine position with the neck extended. Low collar incision and opening of the fascia and splitting of the muscles of the neck were performed. This was followed by ligation of the superior pole of the thyroid lobe with vicryl 0. An advanced energy device was used in all surgeries, either a Harmonic Focus or a LigaSure curved, and a small jaw open sealer/divider shear for dissection of the gland according to the consultants' preference. Identification of the parathyroid glands and recurrent laryngeal nerves

was performed. A suction drain was inserted after good hemostasis.

Follow up

Both groups attended regular follow-up visits after 1 week and then after 1, 3, 6, and 12 months for clinical examination, laboratory follow-up investigations, and ultrasound imaging of the neck.

Statistical analysis

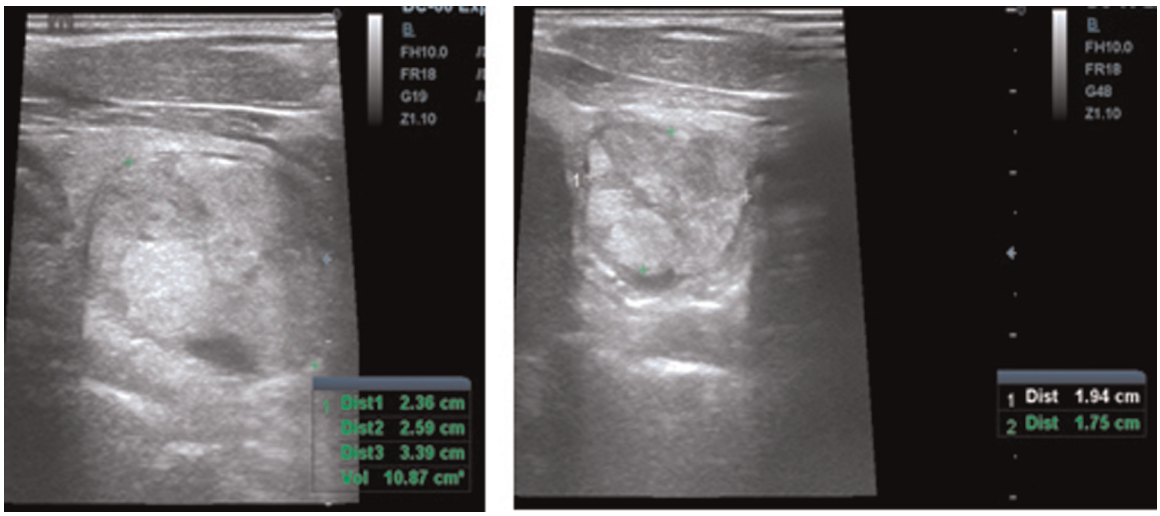
Data were collected, tabulated, and exported to the Statistics Open for ALL (SOFA), version 1.5.3 (statistics were preformed using sofa statistics; Paton-Simpson and associates Ltd., Auckland, New Zealand). Quantitative data were presented as median with SD, while qualitative variables were presented as number and percentages. The comparison of qualitative data was performed using the χ^2 test, while in the case of quantitative data, an independent t test or paired t test was used.

Results

The demographic data (age and sex), the nodule characteristics (maximum diameter, volume, heterogeneity, presence of macrocalcification, and related symptoms), thyroid functions (hyperthyroidism and thyroid-stimulating hormone level) and anti-thyroid antibodies status are reported in Table 1. There were no statistically significant differences between the two groups.

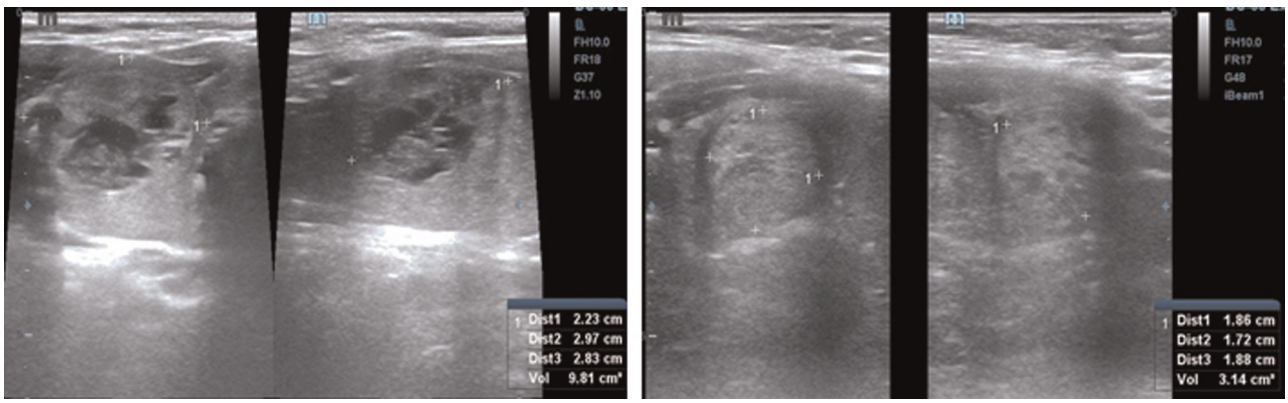
The mean time for RFA was 15.87±12.85 min, while the mean time for surgery was nearly four times longer, with a mean of 66±18.24 min (P<0.001). All patients in group A were managed as day-cases and were discharged 2 h after RFA. However, all the patients in group B were discharged on the following day postsurgery. Return-to-work time was significantly earlier in group A; it was on average 1.91±1.1 days, and it was 10.15±3.16 days in group B (P<0.001).

Figure 1



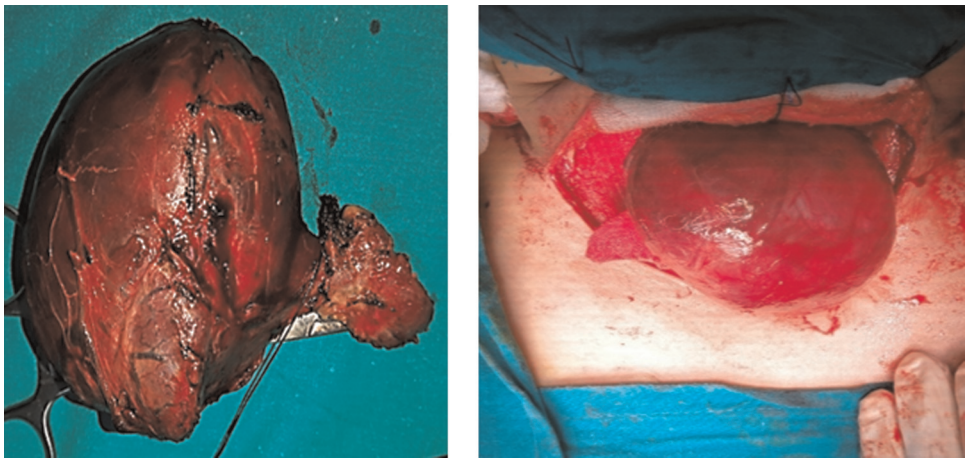
Thyroid nodule before RFA and 1 month after RFA. RFA, radiofrequency ablation.

Figure 2



Thyroid nodule before RFA and 3 months after RFA. RFA, radiofrequency ablation.

Figure 3



Total thyroidectomies for STNs.

Table 1 Preintervention parameters

	Group A (RFA)	Group B (surgery)	*P* value
Age (years)	43.75±10.17	40.54±10.92	0.26
Sex (male/female)	5/19	5/28	0.57
Nodule maximum diameter (mm)	36.57±4.8	35.3±5.74	0.41
Nodule volume	12.41±1.63	11.99±1.96	0.4
Macrocalcifications [*n* (%)]	6 (25)	10 (30.3)	0.66
Neck symptoms [*n* (%)]	17 (70.8)	23 (69.7)	0.62
Hyperthyroidism [*n* (%)]	12 (50)	14 (42.4)	0.57
Heterogeneous nodules	7/17 (29)	9/24 (37.5)	0.875
TSH (μIU/ml)	2.02±1.28	2.2±1.13	0.58
Antibodies [*n* (%)]	1 (4.1)	3 (9)	0.47

RFA, radiofrequency ablation; TSH, thyroid-stimulating hormone.

In group A, 18 patients had one session of RFA, while six patients had two sessions depending on the size of the nodule and patient compliance to the technique. Two patients complained of pain during RFA, which was controlled by stopping the procedure for a little while and by reducing the power. In group B, histopathology was performed after surgery and revealed two cases (6%) with histo-pathological surprise one was papillary and the other was follicular carcinoma.

Follow-up

Early postintervention follow-up was performed 2 h after RFA, before discharge, day 1 after surgery and after 1 week. Postintervention pain using visual analog scale, with a score ranging from 0 to 10, with 0 indicating no pain and 10 indicating the worst pain, and any postoperative observations were reported.

There was a significant difference between both groups in postoperative pain, with the mean visual analog scale score being 3.08±0.881 in group A and 7.09±0.879 in group B ($P<0.001$). Other early postintervention sequelae such as edema, seroma formation, skin burn after RFA, hoarseness of voice, hypocalcemia, dysphagia, and cough showed no significant differences and are listed in Table 2.

During follow-up visits at the 1st, 3rd, 6th, and 12th months, we observed the persistence of neck symptoms after interventions, which was reported in five (31.2%) patients in group A, but none of the patients ($n=23$) in group B ($P<0.001$). Also, the need for continuation on anti-thyroid drugs was reported among seven (58.3%) of the thyrotoxic patients ($n=12$) of group A, but, again, none of the thyrotoxic patients ($n=14$) of group B had to continue anti-thyroid drugs ($P<0.001$). Four (16.7%) patients in group A experienced reappearance of a new nodule other than the original one, but none in group B ($P=0.015$).

In terms of cost estimation for each intervention, RFA costed 20 000 EGP for the first session and 18 000 EGP for the second session. The cost of surgery ranged from 18 000 to 20 000 EGP. The mean cost was 24 500 ±7961 for group A and 19 053±763 for group B ($P<0.001$).

The overall patient satisfaction (compression symptoms related nodules and cosmetic appearance) with the intervention was as follows: 23 (95.8%) patients were satisfied in group A, while 25 (75.7%) patients were satisfied in group B, with a significant difference (P=0.040) (Fig. 4). Other late postintervention sequelae such as hypocalcemia, hypoparathyroidism, hoarseness of voice, loss of high-pitched voice and hypothyroidism, were all nonsignificant and are listed in Table 2.

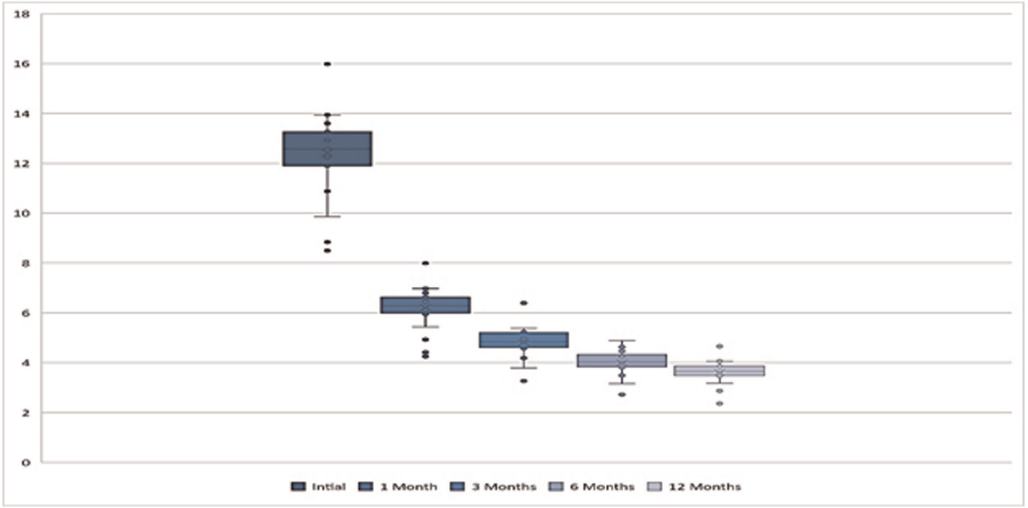
Ultrasound findings during the follow-up period: all patients in group A showed volume reduction in the size of the nodule after RFA, three (12.5%) patients showed progression in size compared with the original nodule; at the 12th month, they were instructed to undergo ultrasound-guided FNAC again to exclude malignant transformation. No criteria suspicious of malignant transformation were fulfilled in our patients, with most of being grade I or II TI-RAD classification. The rate of volume reduction in the size of nodules post-RFA is plotted in Fig. 5. The initial mean volume was 12.41±1.63 ml. One month after RFA, the mean reduced to 6.21±0.81 ml, and this was a statistically significant difference (P<0.001). Further decline occurred after 3, 6, and 12 months, to 4.8±0.66, 3.99±0.52, and 3.61±0.5 ml, respectively. Again, all these reductions showed statistically significant differences when compared with the initial volume reductions. The greatest reduction in volume occurred in the first month, where the nodules reached 50% of the initial volume. Subsequent

Table 2 Early and late postintervention sequelae

Postoperative parameters	Group A=24 (RFA)	Group B=33 (surgery)	*P* value
Early postintervention			
Pain (mean±SD)	3.08±0.881	7.09±0.879	<0.001*
Edema, seroma or skin burn [*n* (%)]	4 (16.6)	6 (18.1)	0.88
Hoarseness of voice [*n* (%)]	1 (4.1)	2 (6)	0.74
Hypocalcemia [*n* (%)]	0	3 (9)	0.12
Dysphagia/cough [*n* (%)]	4 (16.6)	5 (15.1)	0.87
Late postintervention			
Compression symptoms [*n* (%)]	5 (29.4)	0	<0.001*
Reappearance of new nodules [*n* (%)]	4 (16.7)	0	0.015*
Regrowth of the original nodule	3 (12.5)	0	0.036*
Hoarseness of voice or loss of high-pitched voice [*n* (%)]	0	2 (6)	0.21
Continuation on AT medications [*n* (%)]	7/12 (58.3)	0/14	<0.001*
Hypocalcemia/hypoparathyroidism [*n* (%)]	0	1 (3)	0.38
Hypothyroidism [*n* (%)]	1 (4.1)	3 (9)	0.472
Cost (mean±SD)	24 500±7961	19 053±763	<0.001*
Postprocedural satisfaction [*n* (%)]	23 (95.8)	25 (75.7)	0.040*

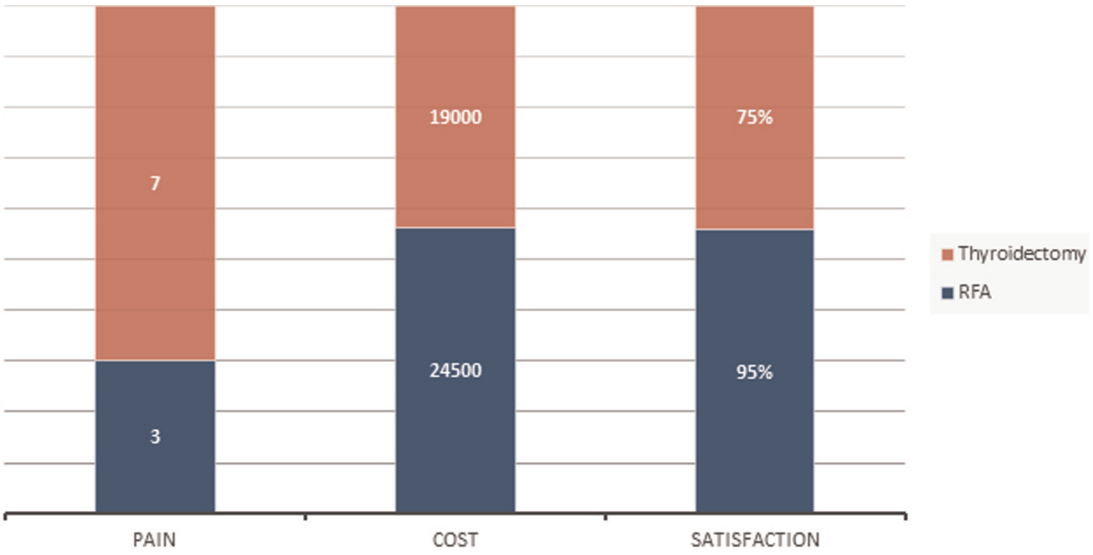
RFA, radiofrequency ablation. *Statistically significant difference.

Figure 4



Difference between both groups in pain, cost, and satisfaction.

Figure 5



Nodules' volume reduction in group A.

reductions in the mean volumes at the 3, 6, and 12 months were 38.7, 32.2, and 29.1% of the initial value, respectively, with *P* value less than 0.001. In group B, ultrasound showed a clear operative bed, with no residual thyroid tissue detected.

Discussion

The prevalence of STN is relatively high. Although surgical treatment is the long-standing solution for these problems, newly developed minimally invasive techniques have been developed for better cosmetic purposes, avoiding general anesthesia in high-risk patients, and to improve the quality of life [16].

The Korean Society of Thyroid Radiology advised to exercise special caution in cases of contralateral vocal cord palsy, pregnant women, and patients with serious health issues as well as patients with cardiac pacemakers or implantable cardioverter-defibrillators to avoid unnecessary risk [17].

During our study, we observed significant differences in volume reduction in the size of the nodule after RFA during follow-up, with the initial volume 12.41 ±1.63 ml reaching 3.61±0.5 ml after 12 months, with serial reduction in between. The highest rate of volume reduction was observed after the first month. There were three (12.5%) patients with progression in size at the 12th month.

Previous studies are in agreement with our studies that RFA can reduce nodule volume by 33–58% after 1 month and by 51–85% after 6 months [13,18]. Baek *et al.* [19] have described a volume reduction ratio of 79% in benign thyroid nodules at 6 months after RFA.

Studies showed that the volume reduction rate of benign thyroid nodules after complete RFA could be more than 50%, and long-term follow-up found that the volume reduction rate of some benign thyroid nodules could even reach 75–97% [20,21].

Although, in our study, most patients had shown improvements after a single session of RFA, others may require a second session to achieve complete ablation. The reduction in nodule volume after RFA has been found to be about 50% at 1 month and 38.7, 32.2, and 29.1% at 3, 6, and 12 months, and this is in agreement with several results of other studies [14,18,19,21,22].

Most of the studies considered the role of RFA in volume reduction, especially the first month after the intervention, even reaching about 93% after 4 years [23], but they neglected the false-negative results that may be obtained with FNAC and its accuracy in diagnosing thyroid neoplasia. In our study, there were two (6%) patients with postsurgical accident.

Stojadinovic *et al.* [24] reported up to 61% inaccuracy in the initial diagnosis when the results of FNA were compared to histology or revised later by an expert cytologist.

Gupta *et al.* [25] FNAC cannot distinguish between follicular adenoma and follicular carcinoma. Here, the

role of surgery appears to be crucial to obtain tissue for histopathology for postoperative correlation with FNAC.

Previous studies have reported that malignancy can be found within a benign nodule. The group of Arora *et al*. [26] analyzed 826 thyroid surgical specimens and discovered eight (2%) carcinomas within benign nodules. In another work, Park *et al*. [27] discovered occult papillary carcinomas in 9.2% of adenomatous goiters and 4.3% of follicular adenomas.

This is in line with the recent study carried out by Wang *et al*. [28], who showed that, on average, 6% of benign nodules are found to be postoperatively malignant by cytopathology diagnosis. These findings clearly demonstrate that some benign nodules may harbor microscopic foci of malignancy that can be missed at the FNAC due to sampling error.

We found significant differences in the pain-related intervention between both groups. Pain is more acceptable in RFA than surgery in the early postoperative sequelae. RFA had a higher cost than surgical therapy, with a significant difference. The overall patient satisfaction in relation to the procedure was significant between both groups; patients who had undergone RFA were mostly satisfied.

41.7% (five) of our patients stopped anti-thyroid medications after RFA, while 58.3% continued anti-thyroid drugs. After 1 year, regrowth was observed in three (12.5%) patients after RFA.

A study was carried out on 54 patients who underwent RFA between June 2008 and November 2013 with pressure symptoms and/or cosmetic problems. All patients were followed up for at least 12 months on three occasions to evaluate an early sign of regrowth; three types of nodule volumes (total volume, ablated volume, and vital volume) were measured and calculated using ultrasonography. Regrowth was defined as more than a 50% increase in the total volume and vital volume increase was defined as more than a 50% increase compared with the previously reported smallest volume on ultrasonography. Increases in vital volume occurred in 31 (57.4%) nodules and there was regrowth in 13 (24.1%) nodules. Vital volume increase tended to precede regrowth [29].

Bernardi *et al*. [30] compared the efficacy, tolerability, and costs of RFA with those of surgery. Their findings showed that RFA was effective for the treatment of nodule-related clinical problems, although surgery was superior for the treatment of large nodules and autonomously functioning nodules.

In terms of postintervention complications, voice change, hypocalcemia, and hypothyroidism, two (6%) patients developed hoarseness of voice, one (3%) patient developed permanent hypocalcemia, and three (9%) patients developed hypothyroidism after surgery, while no patients showed hoarseness of voice or hypocalcemia after RFA, but only one (4.1%) patient had hypothyroidism, with nonsignificant differences between both interventions.

Some studies reported the incidence of hypothyroidism after hemithyroidectomy in about 15% of patients, recurrent laryngeal nerve injury in 0.2–1.1% of patients and permanent hypocalcemia in 1% of patients [31–33].

Vaiman *et al*. [34], after long term follow-up (2–15 years) of 881 patients who had received near total thyroidectomy, found that 100% of the patients had to take thyroxine after surgery and were at risk of developing hypothyroidism if they neglected their replacement therapy. Also, some patients refused surgery because of the possibility of a permanent scar on the neck.

Some studies reported that serious complications such as recurrent laryngeal nerve injury, tracheal injury, bleeding, hematoma, skin lesions, and burns were rare and reversible after RFA, and patients could achieve recovery in long-term follow-up [14,18,35,36].

The 2017 Korean Society of Thyroid Radiology guideline states that RFA is effective in improving thyrotoxic symptoms, hormone levels, and scintigraphy findings in the management of autonomously functioning thyroid nodules. In previous studies, single-session RFA allowed withdrawal of anti-thyroid medication in 21.7–50% of patients. In one study, the anti-thyroid drug dose was reduced after RFA in 78.3% of the patients [37].

The National Institutes of Health Summarized indications of RFA in cases of large (volume >20 ml), nonfunctioning, benign thyroid nodules in patients presenting with local symptoms or cosmetic complaints when surgery is contraindicated or refused, autonomously functioning thyroid nodules, hot/warm at scintigraphy, either toxic or pre-toxic, when surgery

and radioiodine are contraindicated or refused and palliative therapy for recurrent thyroid cancers in the neck when surgery is contraindicated and radioiodine is ineffective [38].

Conclusion

Surgical treatment for a solitary thyroid nodule remains the main line of treatment in view of missed malignancies by FNAC. Surgery is also more effective in abolishing thyrotoxicosis than RFA. However, for high-risk patients or those who refuse surgery, RFA is an effective alternative to surgery that has the advantage of fewer complications and greater patient satisfaction. Keeping in mind the risk of hidden thyroid malignancy, we recommend FNAC periodically for patients with benign thyroid nodules treated with RFA.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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