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REVIEW ARTICLE

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Radiofrequency Ablation of Benign Thyroid Nodules: Initial Review with Clinical Experience in Singapore

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ABSTRACT

Introduction: Up to half of the population may have benign thyroid nodules, and currently surgery is still the mainstay for treatment. However, minimally invasive approaches such as radiofrequency ablation (RFA) have been emerging in clinical practice in recent years. The purpose of this study is to investigate the safety and efficacy of RFA in treating benign thyroid nodules in our local population in Singapore.

Methods: This retrospective study included a cohort of 22 patients (17 female, 5 male), who underwent RFA for benign thyroid nodules at our institute in Singapore, between March 2016 and May 2018. Initial assessment was carried out by ultrasound scanning, to measure pre-RFA nodule diameters, and fine-needle aspiration cytology, to confirm the nodules are histologically benign. Final nodule diameters and post-procedural complications were recorded at 12-months follow-up for all patients. The primary outcome was to investigate a reduction in nodule size, post RFA. The secondary outcome was to investigate any complications/adverse effects up to 12 months post-RFA.

Results: The median nodule diameter reduced from 2.75cm (range: 1.8-7.9cm) pre-RFA, to 1.50cm (range: 0.00 - 1.68cm; p=0.002) post-RFA. No major complications were encountered, however there was one instance of minor post-operative bleeding. There was no regrowth of ablated nodules, no permanent voice changes and no patients were hospitalised post-RFA.

Conclusions: RFA is shown to have substantial efficacy and is associated with fewer post-operative complications than conventional surgical approaches. RFA a promising alternative to surgery, although more research is needed.

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Introduction

A goitre is as an enlargement of the thyroid gland, which may contain nodules (lesions distinct from normal parenchyma). It is estimated that 30-50% of the Singaporean population will show thyroid nodules on ultrasound [1]. Whilst this may seem high, it is often asymptomatic and commonly found on incidental imaging. It is believed that fewer than 5% of these nodules are malignant [1]. Despite that, intervention may be warranted as benign nodules present several problems. Patients could have a visible neck lump, causing cosmetic problems, and may experience symptoms such as pain, dysphagia, dyspnoea, hoarseness, or even systemic thyroid disease. Current management options include active surveillance, especially if the patient is asymptomatic, levothyroxine suppression or surgery. However, risks associated with the latter include neck scars, hypothyroidism as well as the overall risks of general anaesthesia.

The development of minimally invasive methods in the recent years have provided an alternative to surgery in these patients. Current options include laser ablation, ethanol ablation, microwave ablation, and radiofrequency ablation (RFA). RFA, in particular, has been used to treat patients with recurrent thyroid cancers as well as those with symptomatic benign thyroid nodules. The safety and efficacy of RFA for treating benign nodules has been shown in several randomised controlled trials, long-term follow-up studies, systematic reviews and meta-analyses. Comparisons have also

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been made between safety profiles of RFA and surgery that show an overall higher recurrence complication rate with surgery than with RFA [2,3]. There are several papers looking at the Chinese, Korean and European experience with RFA, however, there are no studies looking at its use in the Singaporean population. Hence, this paper is a retrospective single-centre study of the efficacy and complication rate of RFA in patients treated for benign thyroid nodule in Singapore.

Methodology

Patient Monitoring and follow-up

This retrospective study includes 22 patients who underwent RFA from March 2016 to May 2018 at Raffles Hospital, Singapore. This consisted of 17 females and 5 males, with ages ranging 31 to 64 (median age 50.5 years). All patients were initially assessed by ultrasound scanning (USS) and fine-needle aspiration cytology (FNAC) for determining histology and planning treatment. Only patients with histologically-proven benign thyroid nodules were included. All patients had thyroid function tests (TFTs) checked pre-operatively. Associated symptoms on initial visit were classified into: cosmetic, pain, pressure symptoms (difficulty breathing, dysphagia), systemic manifestations of thyroid disease, and increasing size on routine monitoring.

During the follow-up visit, any post-procedure complications were noted and an USS was conducted to monitor any changes in nodule size or number. Data was collected from patient notes and all available follow-up data until November 2018 was recorded. Only patients with adequate follow-up information were included.

RFA Technique

RFA was conducted on an outpatient basis, under local anaesthetic (2% lidocaine hydrochloride). The patient's neck was extended, a trans-isthmic approach was used to insert the electrode, and the "moving-shot" technique was used during ablation.

Statistical Analysis

Results were analysed using IBM SPSS v. 25.0. Data has been displayed as median (range). The difference in nodule sizes pre- and post-RFA has been analysed using the Wilcoxon signed rank test. $p<0.05$ was considered statistically significant.

Results

Pre-Procedural Data

Table 1: Patient demographics upon first visit

Demographic		Frequency
Median age (range)/years		50.5 (31-64)
Sex (M:F)		5:17
Number of symptomatic patients		17
Presenting Symptoms	Cosmetic	10
	Pain	2
	Pressure symptoms	8
	Symptoms of thyroid disease	2
Incidental finding of nodule		2
Increasing size/number of nodules on monitoring		4
Abnormal TFTs		1
Number of patients on levothyroxine		0
Median time from first visit to RFA (range)/ days		80 (3-1920)
Patients with solitary nodules		7
Patients with multiple nodules		15

Efficacy

Median time to initial follow-up was two weeks. Nineteen patients were followed-up within the first-year post-RFA, however, three patients were lost to follow-up. While 22 patients underwent RFA at our centre, only 12 patients had adequate pre- and post-procedure information available regarding nodule dimensions, hence only 12 cases were used for the quantitative analysis of nodule size. The median index nodule diameter was 2.75cm (range: 1.8-7.9cm) prior to any procedure. All patients were found to have smaller nodules by the end of the follow-up period. One-year post-RFA, the median nodule diameter had reduced to 1.50cm (range: 0.00 - 1.68cm; p=0.002), which is shown in figure 1.

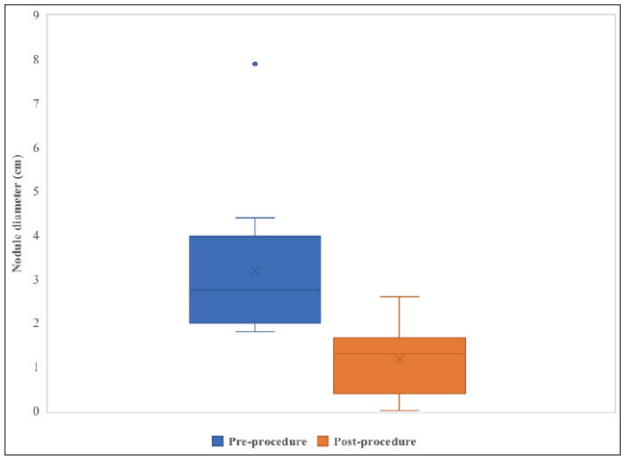

Figure 1

Post-RFA Symptoms

Table 2: Symptoms presented post-RFA

Symptom	Frequency	
	n=	(%)
Re-growth of ablated nodule	0	0.0
Patients with new nodules	3	13.6
Patients requiring hospitalisation post-procedure	0	0.0
Swelling	4	18.2
Post-procedure pain	3	13.6
Hoarseness (transient)	2	9.1
Bleeding	1	4.5
Nodule rupture	0	0.0
Hypothyroidism*	1*	4.5

*2 patients were found to have hypothyroidism during the follow-up period, however, one has been excluded from this count as they were also found to have anti-TPO antibodies and were subsequently diagnosed with Hashimoto's disease.

Discussion

Management of benign thyroid nodules has typically been limited to either active surveillance or surgery. However, the former may not address cosmetic concerns, and the latter is associated with complications such as hypothyroidism, recurrent laryngeal nerve injury and neck scar formation. Hence, minimally invasive options such as RFA are being explored. Our single-centre retrospective series shows a significant reduction in nodule diameter following treatment with RFA, with minimal complications and a short recovery time.

The median nodule diameter in this series reduced from 2.75cm to 1.50cm (figure 1), which is approximately 54.5% of the pre-procedure size, by the 12-month follow-up post-RFA.Several studies in other countries have shown a similar trend in the reduction of nodule sizes following RFA. A South Korean study by Kim, et al. reported volume reduction of thyroid tumours down to 11.8% ±10.9% of original size 9-18.5 months after RFA [4]. Jeong, et al. stated a nodule volume reduction rate of 84.79% at their 6-month follow up post-RFA (n=236).[5] Their mean nodule diameters (2.44±1.36cm pre-RFA and 1.26±1.07 post RFA) are similar to what we present [5].

Conventionally, surgery has been the principal method of intervention for thyroid nodules and goiters [6]. Sun, et al. reported an increase to over 90,000 thyroidectomy procedures performed per year in the USA alone [7]. Depending on the size of the goiter and encroachment of the nodules, the American Thyroid Association (ATA) advises surgical options of a total, sub-total or hemi-thyroidectomy [8]. Total thyroidectomy results in the patient being permanently hypothyroid and dependent on life-long thyroxine replacement. Complications often arise from intraoperative bleeding, given as the thyroid is a highly vascular organ [9]. This can arise from the major thyroid vessels or its parenchyma and consequently obstruct visualization and endanger related structures, such as the recurrent laryngeal nerves and parathyroid glands [9]. Prabhat, et al. studied 364 cases of sub-total/total thyroidectomies reported 59.34% patients experiencing post-operative voice change due to recurrent laryngeal nerve injury, of which 1.85% was permanent [10]. Hoarseness and voice changes have a great bearing on a patients quality of life, and they represent 22.2% of all post-thyroidectomy complications [11]. Although rare, a total thyroidectomy is associated with the risk of bilateral injury of the recurrent laryngeal nerves, resulting in the need for a tracheostomy [8]. Hypocalcaemia is a common complication from injury to the parathyroid glands. Nair, et al. reported the incidence of hypocalcaemia in patients that underwent total thyroidectomy (n=806) as 23.6%, of which 1.61% was permanent hypocalcemia [12].

In addition to a higher complication rate, thyroidectomy complications are shown to be highly dependent on surgeon experience [13]. The complication rate of total thyroidectomies are 14.5% for high-volume surgeons, but 18.8% and 24.1% for intermediate and low volume surgeons [13]. Moreover, over 80% of these operations are performed by intermediate and low volume surgeons [8,14]. A total of 62,722 cases were performed by these different classes of surgeons, resulting in a weighted mean complication rate of 16.4% [13]. Our cases using RFA resulted in a 4.5% complication rate (n=1): one patient was found to have minor peri-lesional bleeding but did not develop a haematoma. We also saw one patient to developed post-RFA hypothyroidism, however they were recorded to be sub-clinically hypothyroid prior to RFA. It should be noted that all patients of thyroidectomies develop hypothyroidism and require life-long hormone replacement. In comparison to the 59.34% of transient hoarseness/voice change reported after sub-total/total thyroidectomies, we saw 9.1% (Table 2) and no cases were permanent [10]. There were no cases of nodule rupture or hospitalisation of patients post-RFA.

Aside from RFA and conventional surgery, there are other modalities available, such as ethanol ablation. Ethanol ablation is a technique that employs the injection of ethanol into the nodules which causes dehydration of epithelial cells and denaturing of proteins [15]. The subsequent actions of coagulative necrosis, fibrosis and small vessel thrombosis cause the eradication of the cyst [15]. The complications associated with ethanol ablation are similar to those of RFA: hoarseness, dyspnoea, temporary hyperthyroidism and so on. A systematic review and meta-analysis conducted by Suh, et al., in 2016 (n=270), reported a complication rate of 5.8% for RFA and 0.8% for ethanol ablation, but this was not shown to be statistically significant (p<0.8479) [16]. Moreover, the review adjusted for publication bias in papers they studied, therefore reporting an adjusted complication rate for RFA of 1.6% [16]. However, what marks a notable difference is the high frequency of patients requiring multiple/repeat procedures to achieve a total cure. Several studies agreed, such as with Jayesh, et al., that stated that this was especially the case for nodules which exceeded 20cc [15]. Bennedbæk, et al. reported only 64% of patients to show a significant reduction in cyst volume after

first treatment using ethanol ablation, and even with multiple treatments, an overall success rate of 82% [17]. Our study found no patients presenting with re-growth of the ablated nodule (Table 2).

There were some limitations with our study: (1) There was only a limited cohort as this was a single-centred study and thus is insufficient to ascertain conclusive evidence, (2) Long-term follow-up was only possible in just over half of our patients as many were from other intuitions, some in foreign countries and (3) the long-run impacts/complications of RFA are difficult to gauge as it has only recently been introduced as a viable treatment for benign thyroid nodules. Both the US and UK deem the safety and efficacy of RFA to be suitable for patients with benign thyroid nodules, as per the ATA and National Institute for Health and Care Excellence (NICE) guidelines [8,18]. NICE recognised that RFA has been used to treat malignant thyroid nodules, but stated there is insufficient evidence to reach a conclusion [18]. In 2017, the Korean Society of Thyroid Radiology published a guideline for RFA, also commissioning its use [19]. Surgery is currently the main modality for intervention in Singapore, however, this may be outdated.

Conclusion

RFA is shown to have a better safety profile than conventional surgical approaches and higher efficacy than alternative techniques, such as ethanol ablation. Our clinical experience in Singapore showed no re-growth of ablated nodules, immense reduction in nodule volume and minimal complications, only of a minor nature. Following the most recent guidelines from other countries, RFA should be considered in the treatment of benign thyroid nodule.

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