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ORIGINAL ARTICLE

Treatment of thyroid nodules with radiofrequency: a 1-year follow-up experience

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Abstract

Purpose The aim of this study is to assess the effectiveness and safety of radiofrequency ablation (RFA) in debulking benign solid thyroid nodules.

Materials and methods This is a retrospective review of 77 patients with predominantly solid thyroid nodules treated with RFA in a single center between 2013 and 2016. All patients declined or were not eligible for surgery. Benign proven thyroid nodules causing compressive symptoms and cosmetic concerns were considered for treatment. Nodule volume, thyroid nodule related compressive symptoms, cosmetic concerns and thyroid function were evaluated.

Results All patients underwent a single treatment session. Mean nodule volume decreased from 17.9 ± 15.6 mL at baseline to 5.2 ± 7.4 after 12 months with a volume reduction ratio (VRR) of $70.9\% \pm 20.8\%$. There were no identifiable factors predictive of response to RFA. Median cosmetic and symptom scores of the entire population decreased from 3 [2–4] and 3 [0–10] to 1 [1–3] ($p < 0.001$) and 0 [0–5] ($p < 0.001$), respectively. No major complications occurred and RFA did not affect thyroid function when normal.

Conclusion RFA induces substantial volume reduction of predominantly solid thyroid nodules and improves compressive symptoms and cosmetic concerns. RFA does not impact normal thyroid function and has an acceptable safety profile.

Keywords Minimally invasive techniques · Thermal ablation therapy · Radiofrequency ablation · Benign thyroid nodules.

Introduction

Over the last decade, minimally invasive percutaneous thermal ablation therapies, such as laser radiofrequency and microwave, have been proposed and introduced into clinical practice to reduce the volume of solid thyroid nodules [1]. Percutaneous laser ablation (LA) has been used since it was first developed and introduced in 1990 [2, 3] as a safe outpatient procedure that effectively reduces the volume of symptomatic solid nodules, improving compressive symptoms and cosmetic concerns in the majority of patients [4, 5]. Since the first report on RFA for the treatment of benign thyroid nodules in 2006 [6] this technique has also been considered to be a safe and effective alternative to surgery [7–12] (although the initial mean nodule volume of the populations treated in the majority of studies was small (< 10 ml) or characterized by a solid component < 50%). The aim of this retrospective review was to assess the effectiveness of RFA on volume reduction of benign thyroid nodules and on improvements in nodule-related compressive and cosmetic concerns. The second aim was to assess the tolerability and side effects of this procedure in the population. Finally the impact of RFA on thyroid function was determined.

Paolo Rabuffi and Enrico Di Stasio equally contributed to the present manuscript.

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Methods

Patients

Data from the clinical records of 77 consecutive patients (55 females; age 57.5 ± 15.5; range 30–75) who underwent RFA in our institution between May 2013 and June 2016 were extracted. Patients were enrolled if they fulfilled all of the following inclusion criteria: over than 18 years of age; presenting with a solid nodule (uniformly compact or nearly completely solid with fluid component ≤ 10%; thyroid nodules with maximum diameter > 2 cm steadily growing over time; evidence at ultrasound examination of a single or a dominant nodule, clearly detectable in a multinodular goiter; cytologically confirmed benign nodule on two separate ultrasound-guided fine-needle aspirations (FNA) biopsy (class TIR 2) [13], with the most recent benign FNA biopsy no earlier than 6 months before the procedure; serum thyroid hormone (free T4 and free T3), thyrotropin levels (TSH), calcitonin, thyroid peroxidase and thyroglobulin antibodies within normal ranges; no history of radioiodine therapy; no previous neck or trunk external beam therapy; refusal of or ineligibility for surgery. Patients were excluded from the treatment in case of pregnancy, of suspicious or cytologically proven malignancy, altered serum TSH and thyroid hormones or coagulation disorders.

Preoperative patient assessment

Sonographic evaluation of the thyroid was conducted by means of a Siemens Sonoline G50 US scanner (Siemens AG, Erlangen, Germany) equipped with a 7.5–13.0 MHz linear transducer. The nodule volume was calculated with the ellipsoid formula ($V = \text{length} \times \text{width} \times \text{depth} \times 0.525$). Serum thyroid-stimulating hormone, free triiodo-thyronine, free thyroxine, antithyroid peroxidase antibodies, and serum calcitonin were determined with commercially available immunoradiometric assay kits. Routine coagulation tests were performed before the procedure and included INR and platelet count. As suggested by other authors [11], we classified nodules according to baseline volume as small (≤ 10 mL), medium (from 10 to 30 mL), or large (> 30 mL). One single nodule per patient was treated with RFA. In patients with multiple nodules, the largest and/or most symptomatic one was treated. Pressure-related and cosmetic symptoms were classified according to a consensus statement [14]; an estimation of pressure-symptoms (such as neck pain or discomfort, cough, foreign body sensation, and dysphagia) was performed via self-evaluation by patients using a visual 10-cm analog scale (grade 0–10 cm). Cosmetic scores were divided into four categories (1—no palpable mass; 2—presence of palpable mass without cosmetic problems; 3—cosmetic problems when swallowing; 4—presence of a widely observable nodule). The protocol for this study was reviewed and approved by the Institutional Review Board (IBR) and was conducted in compliance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standard. Before the procedure was performed, all patients were made aware of possible complications once informed consent was obtained; informed consent was waived for this retrospective investigation.

Procedure

All patients underwent RFA on an outpatient basis. RFA procedure was performed in the angio-suite following sterile preparation. After US examination of the neck, an electrode entry point was chosen and local anesthesia was performed with an injection of 2% lidocaine hydrochloride 2–5 mL and 3 mL of Ropivacaine (Naropine, Fresenius Kabi, USA) from skin-deep to thyroid capsule. The patients underwent conscious sedation through an intravenous infusion of Remifentanil (0.25–1 mcg/kg/min). When multiple nodules were present, the dominant and growing thyroid nodule, thought to be responsible for symptoms, was selected for treatment. We used an RF generator and a 17-Gauge internally cooled electrode with 1-cm active tip (Cool-tip, Covidien, and Mansfield, USA). Generally, after placement of the electrode under US-guidance (US-g) in the desired zone, ablation is initiated at a working setting of 50 W and is then increased in 10 W increments, according to the appearance of a transient hyperechoic zone close to the electrode tip, which is the expression of a temperature of 50–60°C in the target tissue [15]. The ablation time ranged from a minimum of 2 to a maximum of 16 min per nodule (mean time 8 min) We used an oblique approach for electrode placement to position the electrode in the deepest portion of the nodules, followed by subsequent more superficial placement, according to the moving shot technique [7, 16]. This approach along the short axis of the nodule was usually trans-isthmic. We used this approach to treat most nodules. The cranio-caudal approach (along the greatest axis of the nodule) is mostly used in the case of nodules extending into the substernal space or located in a very caudal portion, whereas the lateral approach is rarely used. To keep a safe buffer zone and to avoid the overheating of surrounding critical structures, thus minimizing the risk of complications, the operator maintains the electrode tip at a distance of at least 10 mm from the thyroid capsule and at least 15 mm from surrounding heat-sensitive cervical structures. All treatments were carried out by a team of interventional radiologists involving

three different operators (with a minimum experience in US-guided ablation of 5 years).

Follow-up

Patients were monitored during and immediately after the procedure for any adverse events; subsequently the patient was observed for 2 h and then dismissed. Patients who complained of moderate to severe neck pain or discomfort usually received an oral (Ibuprofen 200 mg) or IV (Paracetamol, 1 gr) painkiller. The definition of complications was consistent with the standardized terminology and reporting criteria for image-guided tumor ablation proposed by other authors [17] and with the classification criteria suggested by the Society of Interventional Radiology (SIR) [18]. Complications were classified as intraprocedural, periprocedural (within 24 h after the maneuver of ablation) and late or postprocedural (in the 30 days following treatment). Thyroid nodules' baseline volume, VRR, thyroid nodule-related compressive symptoms, cosmetic concerns and thyroid function were evaluated at baseline and during follow-up. All patients were given ultrasound examinations (US) at 6 and 12 months. Technical success was defined as $\geq 50\%$ volume reduction at a 6-month follow-up [19].

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD) or median and range, and categorical data as frequencies, where appropriate. The appropriate parametric (ANOVA) or non-parametric test (Kruskal–Wallis ANOVA) was performed to compare different subgroups. Statistical significance was set at $p < 0.05$. Correlation between reduction at 12th month follow-up and volume at baseline was determined by both Pearson and Spearman coefficients. All statistical analyses were performed using GraphPad software (Prism, La Jolla, USA).

Results

All patients underwent a single RFA treatment session, with the exception of one patient who developed a sudden neck haematoma after insertion of the electrode through the thyroid capsule, which required immediate interruption of the treatment. Ablation on this patient was repeated a month later, after complete reabsorption of the haematoma. Table 1 reports the nodules' volume and percentage decrease at baseline, 6th and 12th months after treatment according to initial volume stratification (small, medium and large nodules). Mean nodule volume of the entire population decreased from 17.9 ± 15.6 mL at baseline to 5.2 ± 7.4 (VRR 70.9% ± 20.8%) at 12 months. VRR was similar among nodule classes at the 12th month (70.9–73.4%). Figure 1 reports the dependence of percentage reduction at 12th month on the baseline volume nodule. No significant correlation was detected (Pearson coefficient − 0.09, $p = 0.437$; Spearman coefficient − 0.05, $p = 0.609$). The median and range of cosmetic and symptoms scores according to nodule stratification

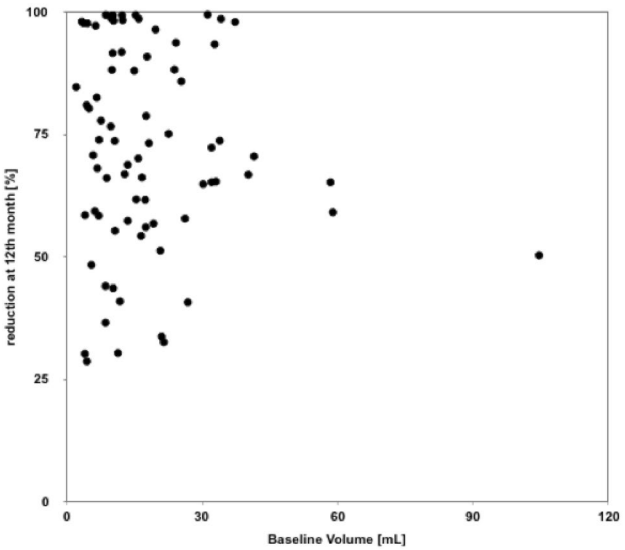

Fig. 1 Dependence of the reduction at 12th month on the volume at baseline. No significant correlation was detected

Table 1 Nodules' volume and percentage decrease at baseline, 6th and 12th months after treatment according to initial volume stratification (small, medium, and large nodules)

Variables	Basal volume (ml)	Volume at 6th month (ml)	VRR at 6th month (%)	Volume at 12th month (ml)	VRR at 12th month (%)
Total population ($n = 77$)	17.9 ± 15.6	6.8 ± 10.4	64.1 ± 20.0%	5.2 ± 7.4	70.95 ± 20.8
Large ($n = 14$)	42.9 ± 20.1	16.3 ± 21.0	68.7 ± 20.8%	12.6 ± 13.4	70.6 ± 16.1
Medium ($n = 38$)	16.4 ± 5.0	6.2 ± 4.0	63.1 ± 20.3	4.8 ± 4.2	70.7 ± 21.6
Small ($n = 25$)	6.4 ± 2.2	2.3 ± 1.3	63.1 ± 19.4	1.7 ± 1.5	73.4 ± 22.5

Table 2 Median and range of cosmetic and symptoms scores according to nodule stratification

	Cosmetic score median [range]			Symptom score median [range]		
	Baseline	6 months	12 months	Baseline	6 months	12 months
Total	3 [2–4]	1 [1–3]	1 [1–3]	3 [0–10]	0 [0–7]	0 [0–5]
Large	4 [3–4]	2 [1–3]	2 [1–3]	7 [4–10]	1.5 [0–7]	1 [0–5]
Medium	3 [2–4]	2 [1–3]	1 [1–2]	3 [0–6]	0 [0–4]	0 [0–3]
Small	2 [2–4]	1 [1–2]	1 [1–2]	1 [0–4]	0 [0–1]	0 [0–1]

Table 3 Changes of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), anti-thyroglobulin (TgAb) and anti-thyroperoxidase (TPOAb) serum levels at 6 and 12 months follow-up

	Baseline	6 months	12months
TSH (0.34–3.2 mcUI/ml)	1.09 ± 0.63	1.45 ± 0.50	1.25 ± 0.49
FT3 (2.3–4.2 pg/ml)	3.03 ± 0.32	3.0 ± 0.9	3.08 ± 0.24
FT4 (0.7–1.48 ng/dl)	1.19 ± 0.21	1.19 ± 0.33	1.32 ± 0.39
TPO Ab (< 35 UI/ml)	37.5 ± 71.9	36.8 ± 69.1	40.2 ± 70.5
TG Ab(< 60 UI/ml)	52.5 ± 45.3	49.7 ± 39.9	51.1 ± 42.9

are shown in Table 2. Median cosmetic and symptoms score of the entire population decreased from 3 [2–4] and 3 [0–10] to 1 [1–3] ($p < 0.001$) and 0 (0–5) ($p < 0.001$), respectively. No immediate or late changes in thyroid function were observed. As shown in Table 3, thyroid-stimulating hormone (TSH), free triiodo-thyronine (FT3), and free thyroxine (FT4) serum levels remained stable. No significant changes were observed in anti-thyroglobulin (TgAb) and anti-thyroperoxidase (TPOAb) antibodies titres during the follow-up period. All patients were euthyroid 12 months after treatment.

Complications and safety

During the RFA procedure, 6 (7.8%) patients complained of pain in the electrode insertion zone and in the jaw area, especially when the electrode working zone was close to the thyroid capsule. The symptoms disappeared after cessation of heat application or after removing the tip of the electrode from the area adjacent to the capsule. No persistent adverse events were observed in the entire cohort during the thermal session, within 24 h or 30 days after the procedure [5, 17]. No patient required unplanned increase in level of care, hospitalization > 48 h, intensive care, surgical repair, or a radiologic interventional approach. We did not observe any late complications (after 30 days). None of the major complications reported by other authors [20], such as voice change, brachial plexus nerve injury, dysphonia or Horner syndrome were observed. Among the minor complications we have had two cases of hematoma. In one case a sudden neck hematoma was observed after insertion of the electrode, which required interruption of the treatment and subsequent immediate manual compression for a few minutes with no hemodynamic sequelae. This haematoma was spontaneously reabsorbed in a month and ablation rescheduled. Another patient developed a subcutaneous perinodular haematoma (of a maximum thickness of 3 cm) in the days following the procedure, which resolved spontaneously after a few days. During follow-up all patients expressed overall satisfaction with the decision to undergo the procedure.

Discussion

The outcome of this retrospective study demonstrated that a single RFA treatment was effective in reducing benign thyroid nodules. A volumetric reduction of 70.9 ± 20.8% at 12 months was achieved. Noteworthy is the fact that the study population was composed of nodules with a liquid portion not greater than 10%. These results are consistent with data from other authors, who have enrolled mainly solid nodules or nodules with a fluid component not exceeding 30% in their studies [9, 11]. In a study evaluating factors predictive of response to RFA, greater effectiveness was present in smaller nodules (≤ 12 mL) [11]. In another study, factors related to superior response to RFA were an initial solid component of ≤ 50% (compared to > 50%) and a smaller initial volume (0–10 mL compared to > 10 mL) [10]. In this series, a substantial homogeneity of results in all three subgroups was observed. In large, medium, and small nodules, a volume reduction of 70.6 ± 16.1%, 70.7 ± 21.6%, and 73.4 ± 22.5%, was, respectively, obtained. Therefore, in this study, no factors correlating with volumetric reduction were found, in particular, the solid composition of the nodule and the initial medium or large nodule volume did not affect the final VRR. In this series, similar to other studies [9, 11], a significant improvement in compressive symptoms and cosmetic concerns (pressure in the neck pressure, difficulty swallowing and cosmetic complaints) was registered in all patients during follow-up. All nodules but one were ablated in a single session, and in no case retreatment was needed. This problem appears controversial and a matter of debate. There is no agreement on the criteria used for repeating RFA. Some authors use more than one treatment

(up to six procedures in some patients) when volume reduction is less than 50% [20] or when resolution of symptoms is incomplete [10]. Others considers a single session satisfactory [20]. Essentially, indications for repeating RFA are currently unclear. All patients maintained previously stable thyroid function after RFA treatment. Surgical therapy for nodular thyroid disease carries the risk of hypothyroidism, and after thyroid lobectomy, thyroid hormone replacement is required in about 15–20% [21, 22]. Lobectomy can pose a 1–2% risk of recurrent laryngeal nerve injury [23]. Additionally, post-surgical scars can be a cosmetic concern for some individuals. Some studies aiming to compare surgery (hemithyroidectomy or thyroidectomy) to RFA for the treatment of benign thyroid nodule have been recently published, but the initial volumes of the nodules treated in these studies were indeed quite small (measuring, respectively, at baseline 12.45 ± 2.52 mL [24] and 5.4 ± 7.1 mL [25]). In patient populations with small and medium nodules, the authors of these studies have recently demonstrated that RFA and surgery were both safe, although RFA has fewer complications and it seems to be less expensive when only one RFA treatment is performed. Indeed, compared to surgery, this technique allows for a shorter treatment period (from 20 min to an hour), according to the baseline thyroid nodule volume [24, 25], fewer complications (an overall complication rate of 1% of RFA versus 6% for surgery, p 0.002) [25], preservation of thyroid function, and fewer hospitalization days [24]. To date, no clinical trials have been performed to evaluate the superiority of RFA vs surgery for the management of large nodules.

Complications

All patients were treated during the procedure with Remifentanil, whose analgesic effects reduce anxiety without provoking sedation, allowing patients to remain vigil and in contact with the radiologist and ensuring a higher degree of collaboration and immobility. Among the side effects, a few patients complained of a painful sensation at the base of the mandible during heat application, which in only one case required interruption of the procedure. It can be surmised that the relatively low complication rate was related, at least in part, to the "subcapsular sparing" approach that was used. In this way the farthest peripheral portion of the nodule was protected from high-temperature ablation, in particular when the electrode tip was close to critical structures (i.e., trachea, carotid artery, jugular vein). The results do not seem to have been affected by this mode of treatment. The overall VRR did not appear to be affected nor reduced, in comparison with most evidence in major publications, and no case of recurrence or regrowth of nodules was observed during our 3-year experience. In addition, another valid explanation may be due to the experience of our team as interventional radiologists. As recently suggested, the operator's specific manual ability in ablative techniques appears to be crucial regardless of the device and technique used [26, 27]. The proper targeting of nodules in close proximity to vital structures such as neck vessels, trachea, and laryngeal nerve requires accomplished manual skill in placing the devices correctly in small anatomical region such as the neck. This problem highlights the importance of appropriate training and learning curves, which should be longer for operators who are not confident with minimally invasive procedures. In light of the above, we underline the need for further studies in this field, focusing in particular on the importance of the operator's experience and background, and on establishing clearer rules for the application of these techniques in the future. This would be crucial for providing the best possible treatment to patients, performed with the most superior techniques, by properly trained physicians.

Limitations

This study has some limitations. First, a relatively small population sample was treated, with an as-yet relatively short follow-up period. Second, data were collected retrospectively. Third, regrowth of treated nodules beyond the period of follow-up was not investigated. Previous studies had reported that marginal incompletely treated vital tissue tends to enlarge after ablation earlier within the first 2 years (recurrence), while later regrowth occurs with a mean timing of 39.9 ± 17.5 months [28]. Despite these limitations, the data appeared homogeneous with regard to efficacy and safety of technique and patient satisfaction.

Conclusions

Data from this study indicate that thermal ablation with RFA is beneficial for patients with benign, predominantly solid thyroid nodules for the prospect of decreasing nodule volume, preserving existing thyroid function, improving compressive symptoms and alleviating cosmetic concerns with a favorable safety profile. Thyroid nodule thermal ablation with RFA has proved to be a safe and effective technique, due to its relatively less invasive approach, low complication rate, and outpatient treatment options.

Compliance with ethical standards

Conflict of interest All other authors have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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