US-CT fusion-guided percutaneous radiofrequency ablation of large substernal benign thyroid nodules

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ABSTRACT

The aim of the present study was to assess feasibility, safety and outcome of ultrasound (US) guided percutaneous radiofrequency (RF) ablation of large substernal benign thyroid nodules assisted by US-computed tomography (CT) fusion imaging and real-time virtual needle tracking (VT) system. Thirty patients (18 females, mean age 56y, range 32–76y) with 35 benign non-functioning thyroid nodules (mean volume ± SD 26.8 ± 7.6 mL; range 20–38mL) were selected for CT-US fusion guided RF ablation. Nodules’ volume was evaluated before treatment and during 12-months follow-up. Complications’ rate was also evaluated. US-CT fusion imaging with VT system was feasible in all cases (feasibility 100%) and it was always possible to complete the procedure as planned (technical success 100%). Minor complications occurred in 2/30 cases (6.6%). No major complications occurred. 50% volume reduction (technique efficacy) was achieved in 93% cases, with a significant mean volume reduction at 12 months follow-up (68.7 ± 10.8%, (p < .001). The VT system could be useful in thyroid nodules ablation procedures assistance being able to track the RF electrode tip even when this is obscured by the bubbles produced by the ablative process. The combination of fusion imaging with VT assisted RF ablation represents a safe, non-surgical treatment option for patients with large substernal benign thyroid nodules.

INTRODUCTION

Thyroid nodules are common findings in general population, with a prevalence of 50% at autopsy [1]. A nodule should be considered to be cervicothoracic (i.e., substernal) when its inferior part presents an expansion penetrating into the mediastinum, passing through the cervicothoracic isthmus and below the subclavian vessels. Thoracic extension is progressive, toward regions of lower anatomic resistance behind and forward of the supra-aortic vessels.

First-line imaging is performed with ultrasound [2] and CT scan is considered the gold-standard for cervicomediastinal exploration [3].

Even if benign, substernal thyroid nodules may require treatment for compressive symptoms or cosmetic reasons [4,5]. Because of its minimal invasive access, percutaneous thermal ablations (including laser ablation (PLA), radiofrequency (RF) ablation, microwave ablation and high-intensity focused ultrasound) are nowadays considered as an effective option to treat benign thyroid nodules and also thyroid cancers [2,6–9]. Ultrasound (US) guided percutaneous ablation techniques are widely described as effective at 12-months follow-up (overall mean volume reduction ranging from 51% to 85%) [9,10] and characterized by low complication rate (0.9–5%) [11–16].

During RF ablation imaging guidance is crucial for precise electrode placement and procedure outcome is strictly related to accurate electrode placement and repositioning [17]. US guidance allows for accurate real-time visualization of the RF electrode and is currently considered the guidance of choice for regular size and location nodule ablation [18,19]. However, when dealing with substernal nodules ultrasound suffers from poor visualization of the deeper aspect of the nodule, of the tracheal margin and also of the vital structures of the ‘danger triangle’ including includes the laryngeal nerve and/or the esophagus [18].

In recent years, new fusion-imaging technologies allowed to merge information from different imaging modalities, i.e., CT and US. These promising technologies consent to combine the panoramic views and the elevated anatomical detail of CT with the ease of use and high availability of ultrasound. Fusion imaging has been described and validated in numerous articles in relation to different districts and pathologies, and in particular in interventional and musculoskeletal radiology [20–23].
Moreover, the approaches utilized to date include the craniocaudal approach along the greatest axis and the transisthmic approach along the short axis of the nodule [18]. When dealing with large and deep nodules, it could be required an almost co-axial insertion of the RF electrode in respect to US probe. This implies a remarkably reduced visibility of the RF electrode at US. Finally, gas bubbles released during thermal treatment may further impair the visibility of the whole procedures [9].

In this setting, the combination of US-CT fusion imaging with virtual needle tracking (VT) systems – that allow for thorough visualization of the whole nodule and improved monitoring of RF electrode tip during the ablation, reducing inaccurate RF electrode placements and complications (burns or direct trauma to the surrounding structures) [13,24]. The use of such devices also enables RF electrode placements with an out-of-plane approach that may be required in some cases.

Fusion imaging and VT have been previously described as a useful guidance for RF ablation [25,26]; however, at our latest knowledge, they have never been used as guidance for substernal thyroid nodules RF ablation.

The purpose of this study is to validate the feasibility of US guided percutaneous RF ablation of large substernal benign thyroid nodules assisted by US-CT fusion imaging and real-time VT system by evaluation of complication rates and 12-months outcome.

Methods and materials

Patients

This retrospective study was approved by the Ethics Committee of the Institutional Review Board with registry number 321/2020. Informed consent for RF ablation and for the current retrospective study was obtained from all patients prior to each procedure.

From September 2016 to May 2021, 119 patients (67 females; mean age 53 y, range 26–78) with 125 benign non-functioning thyroid nodules (mean volume ± SD 14.8 ± 7.5 mL; range 12–38 mL) were prospectively selected for US guided single-session RF ablation. The general inclusion criteria for the treatment were: cytologically confirmed benign nodule on two separate US-guided fine-needle aspiration biopsies (FNAB); compressive symptoms and/or cosmetic issues. All patients had no abnormalities on laboratory tests including complete blood count, blood coagulation battery, and thyrotrophin, thyroid hormones, thyroid autoantibodies and calcitonin.

Among the overall patients, we selected 30 patients (18 females, mean age 56 y, range 32–76 y) which fulfilled the following specific inclusion criteria for the current retrospective study: (1) the presence of a substernal nodule with a volume equal or higher than 20 mL demonstrated by a CT scan; (2) 12 months follow-up including CT assessment of nodule volume, VAS compression score, and cosmetic score.

The exclusion criteria were the presence of a substernal nodule reaching the aortic arch (type 2–4).

A flow diagram of the study is presented in Figure 1.

Pretreatment evaluation

All included patients were evaluated clinically in order to assess the VAS compression value ranging from 0 to 10; and the cosmetic score ranging from 1 (no palpable mass) to 4 (visible mass).

Patients were also evaluated with non-contrast neck CT (Lightspeed 16, GE Healthcare, USA) in order to assess the substernal location of the thyroid nodule and to evaluate its volume and relationship with the surrounding structures. Nodule extension into the mediastinum was performed in the transverse and craniocaudal planes and then classified in four types [27]. The description of transverse extension considered the affected lobes of the thyroid gland and their position into the large thoracic vessels. In addition, nodule extension was considered to be left- or right-sided or bilateral if multiple nodules were present, anterior or posterior, and sited between the trachea and the esophagus or between the esophagus and the vertebral plane. Extension in the craniocaudal plane was considered below the subclavian vessels.

Nodules were classified as: type one (i.e., not reaching the top of the aortic arch); type two (reaching the aortic arch); type three (extending beyond the aortic arch without reaching the carina); and type four (reaching or extending beyond the carina) [27].

The nodule volume (V) was assessed on the WHO classification from 2 orthogonal scan planes using the formula of the ellipsoid (V = length (L) × width (W) × height (H) ÷ 0.524) [28].

All included patients were also evaluated with US (Logiq E10; GE Healthcare, USA) in order to obtain a thorough pre-ablation assessment, including nodule volume and features (e.g., cystic regions, calcifications), approach route for the RF electrode, location and surrounding critical structures (e.g., nerve branches variants, perithyroidal vessels) [29,30].

All radiological examinations were reviewed by a senior radiologist with more than 20 y of experience in head and neck imaging (GT).

CT- US guided RF ablation procedure

Step 1 – US-CT fusion imaging setting

We used the fusion imaging system integrated into the US machine system (V-Nav, LOGIQ-E10; GE Healthcare, USA). This platform has a GPS tracking capability able to generate a three-dimensional operating volume around the patient and two electromagnetic position sensors embedded into the linear probe (6–15 MHz linear ML–6–15, GE Healthcare, USA) (Figure 2(a,b)).

CT images were loaded using standard DICOM format on the US-machine through CD-ROM device.

V-Nav software allowed us to choose the scan series to be merged with the ultrasound image, before and after calibration of the images.

For correct superimposition of US and CT, we defined body landmarks with both imaging techniques such as the apex of the laryngeal incisure of the thyroid cartilage.
We take care to choose body markers on small reproducible landmarks like the lateral margins of the trachea for an accurate identification of the landmarks with both imaging techniques.

The Image calibration occurs through two-step. In the first step, is mandatory to find an ultrasound scan consistent with the orientation of the CT; we placed the probe on a transverse plane at the level of the apex of the laryngeal incisure of the thyroid cartilage.

When the CT scanning plane corresponds to the ultrasound scanning plane and the operator provides the confirmation input, the software connects the CT image to the ultrasound, allowing a synchronous motion, consistent with movements and rotations of the probe.

The second step involves calibrating the anatomical landmarks of the two imaging methods. We have found it convenient to locate the lateral margins of the trachea.

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Once the operator has identified the lateral margins of the trachea, he has to position the cursor over it and confirm the first ‘accuracy point’ the screen will display an icon at the selected point, at the same time both on the CT and US images, which will follow the target thanks to the virtual volume provided by the magnetic field and recorded by position sensors (Figure 3(a,b)). As secondary “accuracy point” the operator could also locate the carotid margins on both imaging modalities and also nodule calcifications, if present.

This allows the operator to have a clear view of the target (the thyroid nodule) even on those substernal and paratracheal locations, otherwise almost invisible with US (Figure 3).

**Step 2 – virtual tracking (VT) setting**

The VT system (VirtuTRAX, CIVCO, USA) was used together with the V-Nav. For the RF electrode tracking a sensor was secured on the shaft of the 18-gauge, 150 mm, fixed RF electrode (STARmed, Korea). The 10 mm active tip was then synchronized with the tracking device by a manual input of the RF electrode length, thus locating the exact position of the RF electrode and projecting its path on the US monitor during the procedure (Figure 4). Thus, the expected RF electrode path is graphically superimposed on the B-mode
image with a line in different colors according to its orientation with the imaging plane.

**Step 3 – nodule ablation procedure**

All patients were treated with 2–5 mL of 2% lidocaine for local anesthesia at the puncture site. No surgical incision was performed in order to avoid any scar formation on patients’ neck. The ablation procedure was performed using a radio-frequency generator (Viva RF generator VRS01, STARmed, Korea). The nodules were treated with the ‘moving shot’ technique [10], inserting the RF electrode in the distal part of the nodule and then moving the RF electrode backwards and upwards with steps of 5–10 s (RF power range between 70 and 80 W in the center of the nodule; 30–40 W in proximity of nodule margins) (Figures 5, and 6(a,b)). The total amount of applied energy was recorded in all patients.

After the procedure, a compressive bandage and ice were applied over the relevant site, and patients were kept under observation for one hour. Then, patients were clinically evaluated in order to detect the presence of voice changes and skin burns. US was used to detect the presence of hematoma. Patients were then discharged from our department.

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*Figure 2.* (a) 6–15 MHz ML-6-15 linear probe, GE Healthcare, USA with needle guide attached through a bracket (arrow); (b) the 18-gauge, 150 mm, fixed RF electrode (STARmed, Korea) equipped with a bracket for the electromagnetic position sensor (asterisk) used to localize it in the volume of space around the patient and to track the needle tip using the V-NAV system.

*Figure 3.* US image (a) and corresponding CT scan (b) of a large thyroid nodule that dislocates laterally the trachea. Note the accuracy point at the lateral margin of the trachea used to synchronize US with TC images. In this case thyroid calcifications were helpful to calibrate the images.
Patients reporting postoperative complications were followed up by clinical visit and US at 10 days to detect if they were resolved.

Follow-Up

A non-contrast neck CT was obtained in all treated patients at 12-months follow-up to be compared with the pretreatment one.

Post-treatment VAS compression score and cosmetic score were also evaluated.

Statistical analysis

We compared pre- and post-treatment clinical and imaging patient’s features using the checklist proposed by Mauri et al. including: (1) Adverse events related to the procedure ranging from A0 (undesired side effects during the procedure with no consequences) to F (death); (2) nodule volume evaluation; (3) nodule volume reduction ratio; (4) VAS compression score; (5) cosmetic score.

Technique efficacy assessed as a volumetric reduction of the 50% of the initial nodule volume was calculated with the formula: 
\[
\frac{\text{final nodule volume}}{\text{initial nodule volume}} \times 100.
\]

Nodules volume at baseline was compared to that at 12-months follow-up using the Wilcoxon test. A \( p \) value of .001 was considered to indicate significance.

Pretreatment VAS compression score was compared to that at 12-months follow-up using the Student’s \( t \) test. A \( p \) value of .05 was considered to indicate significance.

Pretreatment cosmetic score was compared to that at 12-months follow-up using nonparametric methods (Kruskal-Wallis rank sum test). A \( p \) value of .05 was considered to indicate significance.

Results

Following inclusion and exclusion criteria we finally included 30 patients (18 females, mean age 56 y, range 32–76 y) with 35 nodules (mean volume ± SD 26.8 ± 7.6 mL; range 20–38 mL). Type 2–4 nodules were excluded because a safety
margin between the nodule and the aortic arch is required in order to avoid any risk of heating damage to this structure.

Pretreatment VAS compression score and cosmetic score were 8 ± 2 and 4 ± 0 respectively.

RF ablation was performed with a single puncture of the skin in all cases.

In all cases it was possible to perform US_CT fusion and, using the VT system, the tip of the RF electrode was identified during all ablation procedures (feasibility 100%).

It was possible to complete the treatment as planned in all cases (technical success 100%).

We observed side effects (grade A0) in five patients (16.6%) consisting in three patients reporting burning pain during the procedure and two patients reporting significant swallowing impairment at the end of the procedure. All this issues spontaneously resolved at the end of the observation period. We observed two minor complications (6.6%) consisting of a temporary dysphonia and a first-grade skin burn in the site of RF electrode retraction (grade A), all resolved spontaneously in 10 days without delayed complications or cosmetic alterations. No major complications were observed in this series.

Thyroid nodules volume decreased significantly from 26.8 ± 7.6 mL to 10 ± 6.1 mL (p < .001) at 12-months follow-up after ablation, with 50% volume reduction (technique efficacy) achieved in 93% cases and an overall mean volume reduction of 67.3 ± 15.2%, (p < .001).

VAS compression score and cosmetic score significantly improved at 12-months follow-up from 8 ± 2 and 4 ± 0 to 3 ± 3 and 2 ± 2 respectively (p < .05).

Full data are reported in Table 1.

**Table 1.** Clinical and CT evaluation of 35 benign thyroid nodules in 30 patients who underwent RF ablation.

|                           | Baseline       | 12-months follow-up |
|---------------------------|----------------|---------------------|
| Overall (N = 35)          |                |                     |
| Mean volume               | 26.8 ± 7.6 mL  | 10 ± 6.1 mL*        |
| Technique efficacy        | –              | 93%                 |
| Volume reduction          | –              | 68.7 ± 10.8%        |
| VAS compression score     | 8 ± 2          | 3 ± 3*              |
| Cosmetic score            | 4 ± 0          | 2 ± 2*              |
| Major complications       | None           | None                |

*Volume of nodules at 12-months follow-up was significantly lower than that at baseline (p < .001).
*VA compression score and cosmetic score were significantly lower than that at baseline (p < .05% for all).

Discussion

The results of our study demonstrate that IF and VT are feasible and effective for the guidance of RF ablation of thyroid nodules.
nodules with substernal extension and confirm RF ablation as an effective treatment modality for benign thyroid nodules.

The combination of US-CT fusion imaging with virtual needle tracking (VT) systems was successfully used in all procedures, which were all accomplished with a single puncture.

We observed a low adverse event rate in our series with only minor grade A issues and no major complications. This complication rate is consistent with those reported in literature [7–10,13,14,31]. Despite the higher risk of our series related to the poor US visualization of the deep aspect of substernal nodules, thanks to the increased safety given by the combination of fusion imaging and virtual tracking we avoided major complications related to the poor visualization of the RF electrode active tip, especially during ablation of nodules closer to sensible structures (e.g., nerves, vessels, trachea and esophagus).

At 12-months follow-up we observed a technique efficacy higher than 90% without any nodule regrowth requiring an additional RF ablation session. This result, which could be partially explained by the larger baseline nodule volume but also by the increased ablation accuracy furnished by the Fusion/VT system, is comparable or superior with those already reported in literature [16,32,33].

We also observed positive results in terms of clinical outcome, with VAS compression score reduction which was slightly superior with those reported in literature and cosmetic score which was comparable to other series.

These results confirm that RF ablation could be considered a feasible and effective technique also for substernal nodules. This is particularly relevant for those patients affected by severe compression symptoms, which cannot receive surgical procedures because of the presence of comorbidities.

As previously stated by Turtulici et al. we hereby confirm that the use of the VT system, being able to track the RF electrode active tip independently from the US visibility of the RF electrode path, has great potential in providing more accurate and radical sessions of RF ablation in several situations, such as when the RF electrode active tip is obscured due to the bubbles produced during the ablation procedure as well as when the RF electrode active tip is in proximity of the nodule margins, especially for deeper locations.

Moreover, using the newer automatized fusion imaging systems the setting process is not time consuming and is extremely helpful for inexperienced operators, who may take advantage of the more reliable localization of the RF electrode active tip, allowing a shorter learning curve [34].

Finally, in our opinion, the use of US-CT fusion imaging could be particularly helpful for inexperienced operators, who may take advantage of a more reliable localization of the nodule margins and surrounding structures, thus allowing for a shorter learning curve of the whole ablation procedure.

There are several limitations in this study: first of all, the absence of a control group. However, we meant to perform just a feasibility study, as our first goal was to demonstrate that the VT system could be a useful guidance for RF ablation of large substernal thyroid nodules.

Moreover a 12-months follow-up could be considered moderately short but, however, several papers highlights that this is enough to evaluate the outcome of the RF ablation procedure [9,10,28].

In conclusion, the combination of US-CT fusion imaging with VT assisted RF ablation represents a safe, non-surgical treatment option for patients with large substernal benign thyroid nodules.

This technique may improve accuracy and outcome of RF ablation also reducing complications rate of this procedure.

Disclosure statement
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