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Benign thyroid nodules treatment using Percutaneous Laser Ablation (PLA) and Radiofrequency Ablation (RFA)

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On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Abstract

Purpose

To evaluate the reduction over time of benign thyroid nodules treated using percutaneous laser ablation (PLA) and radiofrequency ablation (RFA) by the same equipe.

Materials and Methods

Ninety patients (age 55.6 ± 14.1 years) underwent ablation for benign thyroid nodule causing compression/aesthetic dissatisfaction from 2011. Fifty-nine (age 55.8 ± 14.1 years) underwent RFA and 31 (age 55.2 ± 14.2 years) PLA, ultrasound guided. Technical success, complications, duration of ablation and treatment, energy deployed, volumetric percentage reduction at 1, 6, and 12 months were derived. A regression model for longitudinal measurements was used with random intercept and random slope. Values are expressed as mean \pm standard deviation or N (%).

Results

Technical success was always obtained. No major complications occurred. Mean ablation time was 30.1 ± 13.8 vs 13.9 ± 5.9 minutes ($p < 0.0001$) and mean energy deployment was $5,422.3 \pm 2,484.5$ J vs. $34,662.7 \pm 15,812.3$ J in PLA vs. RFA group. Mean volume reduced from 20.3 ± 16.4 ml to 13.17 ± 10.74 ml ($42\% \pm 17\%$ reduction) at 1 month, 8.7 ± 7.4 ml ($60\% \pm 15\%$ reduction) at 6 months and 7.1 ± 7.7 ml ($70\% \pm 16\%$ reduction) at 12 months In PLA group, and from 32.7 ± 19.5 ml to 17.2 ± 12.9 ml ($51\% \pm 15\%$ reduction) at 1 month, 12.8 ± 9.6 ml ($64\% \pm 14\%$ reduction) at 6 months and 9.9 ± 9.2 ml ($74\% \pm 14\%$ reduction) at 12 months in RFA group. No difference in time course of the relative volume reduction between the two techniques was found.

Conclusions

RFA and PLA are similarly feasible, safe and effective in treating benign thyroid nodules when performed by the same equipe. RFA is faster than PLA but require significantly higher energy.

Keywords

Thyroid nodule, percutaneous ablation, laser, radiofrequency, ultrasound

Introduction

Clinically relevant benign thyroid nodules are more and more frequently treated by image-guided ablations in order to spare thyroidectomy. These strategies have been proven to be effective in achieving nodule shrinkage and relief from clinical symptoms, being also free from major complications [1–5]. Different modalities are nowadays available for image guided ablation of benign thyroid nodules, being RFA [1,2,6], and PLA [3,4,7] the two most widely used. Both modalities have been proven to be effective and free from major complications, with some recent evidence from a meta-analysis of a slight superiority of RFA in terms of volume reduction at 6 months [8]. However, in the mentioned meta-analysis [8], in all the included studies only one ablative modality was applied (i.e. RFA or PLA), and thus the results might have been biased by the different technique used and the operators' experience. Moreover, in that study [8] only nodules with volume < 15 ml were included, which does not reflect the real clinical practice, were larger nodules are often encountered and treated. To the best of our knowledge, there are no papers evaluating the time course of nodule reduction after ablation with the two modalities performed by the same group of operators. This is the aim of our work.

Materials and methods

Institutional review board approval was obtained, and patients' informed consent was waived. We retrospectively evaluated our prospectively collected database of patients treated at two different Institutions by the same group of four interventional radiologists with 5 to 30 years' experience in performing image-guided percutaneous ablations. From 2011, 90 patients (17 males, 73 females, age 55.6 ± 14.1 years) underwent percutaneous thermal ablation of cytologically-proven, benign, Thy2 category thyroid nodule determining pressure symptoms and/or cosmetic problems. All

patients were selected for percutaneous thermal ablation treatment by a multidisciplinary. All procedures were performed with ultrasound (US) guidance under local anesthesia and conscious sedation. In all cases, a preoperative evaluation of the nodule size and shape by B-mode US, and of its vascularization by contrast-enhanced US (CEUS) was performed. At the end of the ablation CEUS was performed in order to immediately assess the result of the ablation [9]. Additional treatment was performed when CEUS demonstrated zones of residual enhancement. A case of treatment of a thyroid nodule with also CEUS assessment is shown in fig. 2.

Percutaneous Laser Ablation technique

According to the procedure previously described [10,11], under US guidance one or two (depending from nodule size and shape) 21G introducer needles were inserted into the target nodule with a dedicated guidance device (EchoLaser X4, Esaote, Genoa, Italy) that allows to insert simultaneously multiple parallel needles regularly spaced. Subsequently, a 300 μ m quartz bare optic fiber was introduced into each introducer needle that was subsequently slightly withdrawn to expose the distal portion (5 mm) of the fiber. The optic fibers were then connected to the laser source (continuous-wave Nd-YAG laser operating at 1.064 μ m, EchoLaser X4; EchoLaser X4, Esaote, Genoa, Italy). The first insertion was always performed into the deeper part of the nodule, with possible subsequent withdrawal to the more superficial portion (so called "pull-back technique"). This allows to limit the number (1 or 2) of direct punctures of the nodule. A fix power protocol (3 watts) was used, changing application time case by case, in order to maintain the power of each single application between 1,200 and 1,800 Joules.

Radiofrequency Ablation technique

For RFA we used an internally cooled, 18G electrode with and 0.5-1.5-cm active tip (AMICA, HS Hospital Service, Aprilia, Italy). The free-hand "moving-shot" technique [12,13] was applied in all cases: the electrode is initially inserted in the deeper portion of the nodule for a short ablation

performed with 40-60 watts power and then withdrawn and repositioned in a different area of the nodule, in order to cover with subsequent ablations the entire volume of the target.

End points and data analysis

Technical success, energy deposition time, total amount of deployed energy, immediate and late complications and volume percentage reduction at 1, 6, and 12 months were recorded. All follow-up US examinations were performed by the same four interventional radiologists who performed the ablations.

Technical success was defined as the ability to complete the treatment that was preoperatively planned. Complications were classified as major or minor according to classification of the Society of Interventional Radiology[14]

A regression model for longitudinal measurements was used with random intercept and random slope. An interaction between time and treatment was considered to investigate the possible difference between the two treatment options in relative volume reduction after the ablation procedure. Statistical computations were performed with R software (R Core Team 2016, R Foundation for Statistical Computing, Vienna, Austria).

Results

The baseline characteristics of patients in PLA and RFA groups are reported in Table 1.

Procedure was feasible in all cases in both groups (technical success 100%).

Mean nodule volume was 28.4 ± 19.4 ml. Fifty-nine patients (11 males, 48 females, age 55.8 ± 14.1) underwent treatment with RFA and 31 (6 males, 25 females, age 55.2 ± 14.2 years) with PLA. Two out of 31 (6.4%) patients in PLA group and three out of 59 (5.1%) patients in RFA group reported mild discomfort during the procedure. One out of 31 (3.2%) patient in PLA group and 1/59 (1.7%) patient in RFA group had a self-limiting peri-glandular small haematoma immediately after the procedure. No late complications occurred. Mean energy deposition time was 30.1 ± 13.8 minutes in PLA group vs 13.9 ± 5.9 minutes in RFA group ($p < 0.0001$). Mean energy deployment was

5,422.3±2,484.5 J in PLA group vs. 34,662.7±15,812.3 J in RFA group ($p<0.0001$). Mean baseline volume was 25.8 (19.4) in PLA group and 20.3 (16.4) in RFA group.

The volume reduction and the relative reduction percentages for each technique at follow up times (1, 6, and 12 months) are reported in Table 2.

According to model results, no evidence for an interaction between PLA/RFA groups and time was found. This means that there is no evidence for a difference in time course of the relative volume reduction between the two techniques. The observed average relative volume reductions at follow-up times (1, 6 and 12) are reported in Figure 1 together with the estimated averages from the regression models (lines). Model results are reported in Table 3. There is a difference between RFA and PLA in average relative reduction at 1 month (treatment: -0.08, $p=0.028$) while the effect of time is the same for both treatment options and is significantly different from 0 (reduction of average relative volume equal to 0.12 per month, $p<0.001$).

Discussion

Our results demonstrate that PLA and RFA are similarly feasible and effective techniques for the treatment of benign (cytologically Thy2) thyroid nodules, with similar results in terms of volumetric reduction at 1, 6, and 12 months and similar complication rates when performed by operators with the same experience.

PLA and RFA have been widely used for performing image guided ablation of benign and malignant tumors[4,15–21]. Even though technical differences have been quite largely studied, no clear evidence of clinical superiority of one technique over the other is present in the literature.

When applied for the treatment of benign thyroid nodules, some technical characteristics and differences in the ablation technique have to be considered. Laser beam has high spatial and temporal coherence, allowing to concentrate and collimate energy over a small focus and minimizing the deposition of energy out of the target, in patients' body. Accordingly, each very thin laser fiber allows to achieve areas of coagulative necrosis of highly reproducible size, in the range of 2 cm in diameter. In addition, with dedicated needle guidance devices, multiple, regularly spaced fibers can easily be simultaneously positioned in order to achieve larger ablation volumes.

Differently, RFA generates heat through high- frequency alternating current. Patients are included in a close-loop circuit (electrode, generator and grounding pads), therefore part of the energy is deposited into patient's body. RF electrodes are larger than laser fibers and in order to apply the moving-shot technique ablation has to be performed by free-hand. This allows for a more personal tailoring of the treatment case by case, but on the other hand seems to require higher technical expertise.

To the best of our knowledge, all the clinical series reported in literature on thyroid ablation describe the results achieved with a single technique, and no studies reports on the results of RFA and PLA performed in the same centre by the same operators. Only recently, Ha et al. performed a meta-analysis comparing RFA and PLA for the treatment of thyroid nodules, including data of 10 papers for a total number of 184 patients [8]. They found a 77.8% pooled percentage mean volume reduction at 6 months in RFA compared with 49.5% in PLA, concluding that RFA appears to be superior to PLA in reducing benign solid thyroid nodule volume. This study currently represents the best available evidence comparing RFA and PLA treatment efficacy of benign solid thyroid nodules. However, in that study [8], only one ablative modality was used in each original included paper, and thus the results might have been biased by the different technique used and the variable operators' experience. Moreover, only nodules with volume < 15 ml were included, which does not reflect the real clinical practice, were larger nodules are often encountered and treated. Thus, to the best of our knowledge, our study is the first in literature directly comparing RFA and PLA performed by the same operators. Particularly, in our series all the procedures were performed by interventional radiologists who started together to perform thyroid ablation, and developed together a common technique and expertise on this kind of procedures, thus theoretically limiting the possible influence of different expertise. In our series, the procedures were always successfully performed with both techniques, and similar significant volume reductions were achieved in both groups in similar time course.

Only one patient in each group had a perithyroidal haematoma that did not require any treatment. Energy deposition time was significantly shorter in the RFA group than in the PLA group.

However, with RFA multiple electrode repositioning is necessary, thus the overall procedural time may be more affected by the operator's experience. On the other hand, energy deployed was significantly higher in the RFA group than in the PLA group. Systemic effects related to the energy delivered through percutaneous ablations have been occasionally reported, and investigated mainly in preclinical study and for liver disease [22-24]. Particularly, oncogenesis has been reported as an off-target effect of radiofrequency ablation [22-24], but clear relationship with different ablative methods, the total deployed energy or time of ablation has not been fully investigated yet. Thus, even though very few data exist on the systemic effects of thermal ablations, this aspect cannot be totally neglected when comparing the effects of different ablative modalities which, as in the present study, show highly different energy deposition profile.

All our procedures were performed by two of four interventional radiologists with a long experience in image-guided treatments, using the most advanced imaging equipment and CEUS for the immediate assessment of the result achieved in all cases. As during ablation gas production might limit visualisation, availability of most recent imaging equipment is crucial. This seems to be particularly important in RFA, as with this technique gas formation seems to be higher [25]. Some authors, in order to enhance the needle visualisation during ablation, proposed to use fusion imaging and virtual needle tracking [6]. Particularly, as showed in Fig. 2, the use of CEUS at the end of the procedure can be useful for the intraoperative assessment of the coagulative necrosis volume achieved, in order to decide whether or not perform a further ablation [9]. This may have had a not negligible influence in our results, as the operator's experience and ability to complete the treatment in case of incomplete ablation can affect the final result more than the technique used.

Our study has some limitations. First, we retrospectively analyzed our prospectively collected data in a small number of patients, which may not be sufficient to demonstrate a statistical difference in the two groups. Moreover, patients were not randomly assigned to the PLA or RFA group and the pre-treatment mean nodule volume was statistically higher in the RFA group than in the PLA group. Third, patients were treated by operators with high experience in performing image guided

procedures, and our results may not reflect the general practice. Last, we only focused on 12-month follow-up, not having data about long term results as yet. Further, possibly multicenter and prospective studies on larger patients' series are needed in order to clarify all the still questionable issues.

Conclusion

In conclusion, RFA and PLA are similarly feasible, safe and effective in the treatment of benign thyroid nodules when performed by the same highly experienced operators.

Declaration of Interest

Author #1: the author report no conflicts of interest.

Author #2: the author report no conflicts of interest.

Author #3: the author report no conflicts of interest.

Author #4: the author report no conflicts of interest.

Author #5: the author report no conflicts of interest.

Author #6: the author report no conflicts of interest.

Author #7: the author report no conflicts of interest.

Author #8: the author report no conflicts of interest.

Author #9: the author report no conflicts of interest.

Author #10: the author report no conflicts of interest.

Author #11: the author report no conflicts of interest.

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Table 1 - Baseline characteristics of 90 patients who underwent percutaneous laser ablation or radiofrequency ablation of benign thyroid nodules.

	Overall (90 patients)	PLA group (59 patients)	RFA group (31 patients)	
Sex (M) *	17 (0.19)	6 (0.19)	11 (0.19)	$p^*=1.000$
Age (years)**	55.6±14.1	55.2±14.2	55.8±14.1	$p=0.836$
Complications (Yes)*	2 (0.02)	1 (0.02)	1 (0.03)	$p=1.000$
Volume (ml) **	28.5±19.4	20.3±16.4	32.7±19.5	$p=0.003$
Ablation time (min)**	19.5±12.2	30.1±13.8	13.8±5.9	$p<0.001$
Deployed energy (J)**	24,5910±18,980	5,422.2±2,484.5	34,662.7±15,812.2	$p<0.001$

Values are expressed as mean ± standard deviation or N (%);

* Fisher's exact test;

** Student *t*-test.

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Table 2 - Volume reduction and relative reduction percentages for each technique at follow up times

	Overall (90 patients)	PLA group (59 patients)	RFA group (31 patients)
<i>Pre-treatment</i>	28.5±19.4	20.3±16.4	32.7±19.5
<i>1 month</i>	15.7±12.2	13.2±10.7	17.1±12.9
<i>% relative reduction</i>	48%±16%	42%±17%	51%±15%
<i>6 months</i>	11.1±8.9	8.7±7.4	12.9±9.6
<i>% relative reduction</i>	62%±14%	60%±15%	64%±14%
<i>12 months</i>	8.7±8.6	7.1±7.7	9.9±9.2
<i>% relative reduction</i>	72%±15%	70%±16%	74%±14%

Table 3 - Regression model for longitudinal measurements results

	Value	SE	DF	t-value	P-value
Intercept	-0.45	0.03	113	-15.41	<0.001
Treatment	-0.08	0.04	55	-2.25	0.028
Time	-0.12	0.01	113	-12.55	<0.001

Figure 1 - Observed average relative volume reductions at follow-up times (1, 6 and 12 months) and estimated averages from the regression models (lines)

Figure 2 - Treatment of a benign thyroid nodule with percutaneous image guided laser ablation. **A** Ultrasound evaluation of a benign thyroid nodule before ablation. **B** Contrast-enhanced ultrasound before ablation demonstrating enhancement of the nodule. **C** Insertion of two laser fibers into the nodule. Dotted lines indicates different possible trajectory of the needles; green and yellow lines indicate the position of the two inserted fibers; blue line show the expected ablated area. **D** Pull-back of the two fibers to enlarge the ablation zone. Hyperechoic aspect of the central part of the nodule is due to gas formation during the ablation. Dotted lines indicates trajectory of the needles; green and yellow lines indicate the position of the two inserted fibers; blue line show the expected ablated area. **E** Contrast-enhanced ultrasound demonstrating lack of enhancement in the ablated area. **F** Ultrasound of the treated nodule at 6 months demonstrating significant volume reduction.

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