Peer Review File

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Review Comments (Round 1)

Reviewer A

The authors report on the limited scope of the existing literature regarding radiofrequency ablation of autonomously functioning thyroid nodules (AFTN). The references are up to date, the conclusions are well explained and the extent of the article is appropriate. Only two questions remain open for discussion:

Comment 1: Line 170 - "the lower of inducing ..." It seems as there is a word omitted, e.g. "risk of inducing ..." or "probability of inducing ..."

Reply 1: Thank you for your kind comments regarding our manuscript. We have added "risk" to the phrase.

Changes in the text: line 170

Comment 2: Line 191/192 - " ... RFA does not resolve thyroid dysfunction ..."

The authors cite two references doubting the value of post-ablation scintigraphy, and consider RFA eventually ineffective as it "does not resolve thyroid dysfunction". The context is however that scintigraphy remains at date the accepted gold standard of diagnosing AFTN, and turning a hot nodule into a cold one should indicate effective RFA treatment. Finding risk factors for treatment failure in uni- and multivariate analysis will be a major task for future research. The authors are requested to comment on this thesis.

Reply 2: Thank you for your thoughtful comment. We agree that the role of scintigraphy is the gold standard of AFTN diagnosis, however the role of scintigraphy after RFA has not been established. Because RFA does not result in ablation of 100% of the AFTN (biochemical and symptom resolution typically occur at 70-80% VRR), there is a chance of regrowth which is seen in the literature for benign, nonfunctioning thyroid nodules. There is a greater volume of literature regarding benign nodules with longer follow up and regrowth noted as early as 2-3 years post ablation.

Changes in the text: lines 202-207

Reviewer B

This is a nice systematic review from prospective and retrospective thyroid RFA publication. since we only have few RCT for thyroid RFA. so for me this manuscript is sufficient to be published. but before its better for you to revise truncated table 2. you also need to mention the conclusions in the main body, other than those contained in the abstract.

Reply: Thank you for your kind comments. We have revised the table to be more consistent and clearer.

Reviewer C

Comment 1: One of the concerns I have about this review is the relative weightage of the outcome measures. For autonomously functioning thyroid nodules the goal of therapy is to resolve the hyperthyroidism (or subclinical hyperthyroidism) and not so much volume reduction. As such, a ~ 50% volume reduction that does not result in restoring euthyroid state is not considered success. Typically, most nodules will need a volume reduction of at least 70 – 80% to achieve euthyroidism.

Reply 1: Thank you for your comments. We have updated the manuscript to include a volume reduction rate of 70-80% to reflect meaningful reduction in hyperthyroidism.

Changes in the text: lines 99-100, 102

Comment 2: Comments regarding Table 2:

The table is cut off the page so not completely visible and some attention should be paid to formatting (% is front of some numbers and not others). Abbreviation should be VR = volume reduction; a ratio is when you don't multiply it by 100; if you multiply it by a 100 it's a percentage. Kim, et al 2021 should be listed separately as it's a systematic review and Cesareo, et al's 2019 meta-analysis with 8 studies should also be included. Largest series from United State with 24 AFTNs (Hussain, et al, 2021) should also be included. The follow-up period of these studies should also be noted in the table. A separate table indicating the studies comparing different treatment modalities should also be made.

Reply 2: Thank you for your comments. The text, table 2, and figure 1 have been updated to reflect that we are looking at a rate and not a ratio. The units

throughout the table have also been adjusted per your formatting recommendations. Both Cesareo et al. (2020) and Hussain et al. (2021) have been added to table 2 as well as a column dedicated to follow up time. Because there are only two meta-analyses, these have been included in table 2 instead of making a new table. The authors agree that a comparison of all treatment modalities would be an excellent addition, however we are limited in the number of tables. We also plan to look into an outcome comparison in the future which would include such a table.
Changes in the text: Lines 99 and 101, Table 2 and Figure 1.

Comment 3: Line 47 - 48: "treatment", "procedure" or "session" rather than dose.
Reply 3: Thank you for your comment. The word "dose" has been replaced with "session"
Changes in text: line 47

Comment 4: Line 50: I'm not actually aware of any reported patients requiring long term levothyroxine therapy. Avoiding permanent hypothyroidism is one of the main reasons for choosing this procedure.
Reply: Thank you for your comment, we have altered the text per your recommendations.
Changes in the text: lines 50-51

Comment 5: Line 54 – 50: Would be more specific about what additional data/studies are needed and why the current data is not sufficient to prove long term efficacy. Should we compare to surgery? To RAI? Follow for 5 years? 10 year? Why?
Reply 5: Thank you for your comment. As these lines are included in the abstract, additional details can be found in the "Areas of Future Research" in the main body of the manuscript.
Changes in the text: none

Comment 6: Line 60: Would be consistent with terminology – either toxic thyroid nodules or autonomously functioning thyroid nodules (preferred).
Reply 6: Thank you for your comment, our terminology has been updated per

your recommendations
Changes in the text: line 61

Comment 7: Line 67: Anti-thyroid medications are effective in the long term – they are just not preferred because patients need to be monitored more frequently with dosage adjustments, there is risk of agranulocytosis or liver failure and patients with AFTN do not go into remission so they have to be on the medications lifelong, unlike patients with Graves' disease.
Reply 7: Thank you for your comment. In accordance with the 2016 ATA guidelines, ATM's are not recommended long term therapy unless the patient is unable to tolerate surgery or near the end of their life, "Long-term MMI treatment of TMNG or TA might be indicated in some elderly or otherwise ill patients with limited life expectancy, in patients who are not good candidates for surgery or ablative therapy, and in patients who prefer this option."
Changes in the text: lines 66-68

Comment 8: Line 68: May require rather than often requires – although would prefer that the authors actually include how smaller nodules respond to RAI compared to larger nodules, as initial size of the nodule is also relevant to treatment with RFA.
Reply 8: Thank you for your comment. That is a great point that will need to be examined in a separate study as there is no literature reporting the differences in outcomes between the two modalities. This manuscript was intended to be a review of the efficacy RFA.
Changes in the text: none

Comment 9: Line 72: Would not call RFA a definitive option (which would be surgery) but rather an alternative option.
Reply 9: Thank you for the correction. The authors agree and the text has been updated to reflect your comment
Changes in the text: line 74

Comment 10: Line 94 - 95: 0.5 is a ratio; 50% is a percentage – would just use the term volume reduction. However, a volume reduction of 50% is not a marker of success

in AFTN. If the patient is still hyperthyroid then the procedure is not successful regardless of the volume reduction.

Reply 10: Thank you for your comments. Rereview of the literature is consistent with resolution of hyperthyroidism associated with 70-80% volume reduction. The text and citations have been updated.

Changes in the text: lines 97-99

Comment 11: Line 109 – 110: The studies actually do not show any differences based on solid vs cystic components; however the initial nodule size influences the response (in the same way as non-functional thyroid nodules i.e. smaller nodule respond better).

Reply 11: Thank you for your comments, the text has been updated to reflect your comment

Changes in the text: lines 113-114

Comment 12: Line 111 – 113: Would like more clarity on the relative vascularity of AFTN vs non-functioning thyroid nodules. AFTN require a more complete ablation and higher volume reduction which is way vascular techniques such as artery first and marginal vein ablation have been advocated for. Complete ablation should be stressed and more details should be given regarding the why and how.

Reply 12: Thank you for your comment, discussion of why one would consider these techniques has been added to the text.

Changes in the text: lines 116-119

Comment 13: Line 114: This section should include discussion on why some studies had a very poor success rate e.g. Deandra, et al 2008, and how outcomes compare to surgical resection and radioactive iodine – several studies listed in table 2 show an overall worse success rate for RFA compared to the success rate of RAI reported in the literature.

Reply 13: Thank you for pointing this out. Upon review, the results previously listed for Deandra et al. were erroneous. TSH normalization occurred in 78% of patients and improvement occurred in 100% of patients with AFTN.

Changes in the text: Table 2 has been updated.

Comment 14: Line 115 – 116: This is the main treatment outcome – the whole reason you're treating the patient in the first place.

Reply 14: Thank you for your comment. The text has been updated to reflect your comment.

Changes in the text: line 121

Comment 15: Line 126 – 127: Please distinguish between symptoms of hyperthyroidism vs compressive systems. Most AFTNs are diagnosed prior to them becoming large enough to develop compressive symptoms because they affect thyroid function. Volume reduction in a AFTN is only a measure of success in AFTN if it was causing compressive symptoms; and it's an indirect measure of success otherwise as more volume reduction results in more likelihood of achieving euthyroidism.

Reply 15: Thank you for the above comments. Compressive symptoms are not mentioned in our manuscript, only "cosmesis," which is used in the literature as a subjective, patient provided endpoint. We did not find documentation of AFTNs causing compressive symptoms.

Changes in the text: none

Comment 16: Line 137: Would add the time frames when regrowth is expected in benign thyroid nodules – AFTN will probably follow the same time line as non-functional thyroid nodules so regrow is likely to occur after 3 – 5 years.

Reply 16: Thank you for your comment. Regrowth can be seen as early as 2-3 years after RFA in benign nodules.

Changes in the text: lines 147-148

Comment 17: Line 144: Are there any actual reports of Horner syndrome? In an AFTN? Horner's syndrome has typically occurred when ablating a malignant nodule in the posterior part of the neck. What are the details of the patient who developed permanent hypothyroid? Did they has Hashimoto's thyroiditis and thus higher risk of developing hypothyroidism spontaneously anyway?

Reply 17: Thank you for your comment. The authors found a case report by Hamou and Monpeyssen published in ACCR in which a patient with a nonfunctioning, benign thyroid nodule underwent RFA and subsewuently

developed ipsilateral ptosis and experienced <50% VRR. The authors of this case report considered this a technical failure.
Changes in the text: none

Comment 18: Line 149: Whether thyroid rupture is managed conservatively or not usually depends on whether it has become infected or not and how symptomatic is it. The reference quoted indicates when thyroid nodules with an initial size of more than 4.5 cm in maximum diameter have a thyroid rupture they are more likely to require invasive management i.e. longer procedure times and higher initial nodule volume are associated with needing more invasive treatment. This doesn't really come across in the way it is worded.
Reply 18: Thank you for your comment, this has been clarified per your recommendations
Changes in the text: lines 156-157

Comment 19: Line 169 - 170: RAI is covered by insurance however it is not necessarily cheaper (cost of I-131 dose, NM uptake and scan, radiology and facility fee, etc). "lower risk of"
Reply 19: Thank you for your comment, this has been updated per your recommendations
Changes in the text: line 178

Comment 20: Line 174 – 175: Please clarify what this means? Why can't the post-operative hypothyroidism and complication rate "be performed"? The post-operative hypothyroidism rate of a total thyroidectomy is 100%, etc.
Reply 20: Thank you for your comment. Comparison of rates of hypothyroidism after RFA v lobectomy would be more compelling than RFA v total thyroidectomy as RFA does not target the entire thyroid.
Changes in the text: lines 184-185

Comment 21: Line 178 – 181: This is not specific to AFTN and more relevant to non-functional thyroid nodules. It should be concerning if the patient becomes hyperthyroid again regardless of the increase in nodule volume. The definition of residual rate is

unclear – and unless this a per unit of time it is not a rate.

Reply 21: Thank you for your comment. The reference to nonfunctioning nodules has been added and the line regarding residual rate has been removed

Changes in the text: lines 189-194

Comment 22: Line 191 – 192: In the nodules where it does not resolve thyroid dysfunction – I would just call that an unsuccessful procedure rather than an area of future research. The reason it doesn't resolve is because enough of the functional thyroid tissue was not ablated (again coming back to the point that 50% volume reduction doesn't necessarily indicate success.

Reply 22: Thank you for your comment, these lines have been removed from the text.

Changes in the text: lines 206-207

<u>Review Comments (Round 2)</u>

Comment: Thank you very much for the opportunity to re-review the above manuscript. I consider the manuscript in its present form ready for publication in Gland Surgery, since it is well written, the references are appropriate and the conclusions are sound. It is okay to raise a critical appraisal in this topic.

This is however a rare case where I have less reason to criticize the manuscript, albeit I disagree with the response to the reviewer. In fact, whereas it is usually not intended to ablate 100 % of the nodule volume in benign thyroid nodules, autonomously functioning thyroid nodules (AFTN) as well as papillary thyroid micro carcinoma (PTMC) are the rare exceptions.

As the chance to ablate the target volume completely decreases with its size, ablation of small AFTN works best. This is reported in the narrative review and endorsed by the references. The remaining open question is the threshold up to which volume thermoablation can be recommended at date. I regret not to read anything about that in the Conclusions.

Reply: Thank you for your endorsement for this manuscript. The authors believe that the question the reviewer is asking is regarding the maximum nodule size for which ablation can be considered effective or advantageous to the patient. Most published data

found by the authors pertained to small nodules (as documented in the manuscript). With the increasing popularity of RFA, we can hope that more data will become available for study.