Peer Review File

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Reviewer A

Comment 1: 1. Introduction
Line 51: 7% to 15% harbor malignancy
Most of the data showed the malignant rate of thyroid nodule is around 5%. Please cite reference to support your point.

Reply 1: Thank you for pointing this out. This particular malignancy rate is obtained from the American Thyroid Association 2015 guidelines and is now cited in the text (line 4).

Comment 2: Principles of Radiofrequency Ablation
In thyroid RFA, moving shot technique is commonly used and friction heat is more important than conductive effect by using moving shot technique.
Please brief introduce moving shot technique.

Reply 2: Thank you for these comments. Moving shot technique is now included in the text, lines 35-38.
"To assure safe treatment of the entire nodule, the trans-isthmic moving shot technique is employed.[8] The active probe is introduced through the isthmus and positioned in the deepest portion of the nodule. Ablation proceeds as the tip is withdrawn as evidence of echogenic change is witnessed on ultrasound.[8]"

We also removed the reference to conductive heat to keep the focus on frictional heat as the more important effect.

Comment 3: Benign Thyroid Nodules

Some literatures have investigated the role of RFA for patients previously receiving lobectomy, partial thyroidectomy or with bilateral thyroid nodules. Please review this.
Even rare, some patients still suffered from thyroid dysfunction after RFA. Please discuss this issue.
Nodular rupture after RFA is also another important issue, please discuss this.

Reply 3: We appreciate suggesting the addition of these important points. They are addressed individually below.
Information and reference to RFA and prior thyroid surgery or bilateral nodularity has now been included in lines 65-69. "RFA can also be an effective option in the setting of prior thyroid surgery. In a study of 20 patients with history of previous thyroid lobectomy, RFA achieved reduction of 85.41% with no effect on pre-procedure thyroid hormone status.[19] Bilateral nodules may also be treated effectively, though separate sessions are recommended to maximize ablative efficacy and safety.[20]"

The section regarding hypothyroidism after RFA has been expanded in lines 71-83. There are currently two studies referenced regarding low prevalence of hypothyroidism, and we have also added discussion of risk factors for developing this post procedure. "A primary advantage of RFA is the preservation of normal thyroid parenchyma, which results in the low risk of hypothyroidism in long term follow up.[15] A 2014 study of 111 patients treated with RFA or lobectomy reported 23% of surgical patients required daily thyroid hormone, while no patients in the RFA group became hypothyroid post-procedurally.[21] Risk factors for long-term post-RFA hypothyroidism include lower baseline thyroid stimulating hormone (TSH) levels and the presence of thyroid peroxidase antibodies.[22]"

Nodule rupture is now discussed in lines 84-86. "Unique to RFA, nodule rupture may rarely occur weeks to months following RFA, and presents as a sudden painful neck swelling. Most cases of rupture may be treated conservatively.[23]"

Comment 4: Autonomously Functioning Thyroid Nodules
Should the patients restore euthyroid status before RFA?

Reply 4: This is an excellent point, and not a pre-requisite that has been discussed in the literature to date, as far as the authors are aware.

Comment 5: Line 141: The simultaneous acceleration of thyroid molecular testing. Please cite reference.

Reply 5: This is now cited in the text, line 131.

Comment 6: Recurrent Malignant Lesions
Line 153: Kim et al. Please cite reference

Reply 6: This is now cited in the text, line 146.

Comment 7: Regarding voice change, some authors have published some methods to deal with this problem. Please introduce this.

Reply 7: An introduction to this concept has been introduced in lines 152-153. "Strategies to mitigate voice change have been proposed, including instillation of cold dextrose in the tracheoesophageal groove until the voice has normalized.[36]"

Reviewer B:

Comment 1. Line 51 - 52: Please give reference for percentage of malignant thyroid nodules.

Reply 1: This is now cited in the text, line 4.

Comment 2. Line 67 – 68: Please give reference or evidence of RFA's popularity worldwide compare to other thermal ablation techniques. If there are regional differences in popularity of different techniques then please briefly outline these.

Reply 2: RFA's global adoption was described by Kuo et al and is now included as the citation in line 20. Anecdotally, there do seem to be regional differences in preference for thermal ablative approach. However, as far as the authors are aware, there is not literature yet available describing these differences and preferences.

Comment 3. Line 74: Please re-write for clarity: "water content will vaporize and the tissue will desiccate"

Reply 3: This has been changed to read as follows: "Above 100°C, water vaporization and tissue carbonization occur."

Comment 4. Line 74 – 76: Please re-write for clarity describing exactly how the thermal conduction is impaired and what negative consequence this has on the RFA procedure. And change target temperature to 50 – 90 °C.

Reply 4: This has been changed to read as follows: "This creates char and coagulum at the active tip of the probe, which impairs further ablation. Therefore, intermediate temperatures of 50°C-90°C are targeted.[6]"

Comment 5. Line 78: Please change to "generate heat via ionic friction"

Reply 5: This has been changed as follows: "RFA relies on an alternating current at the active tip of a probe inserted under ultrasound guidance to generate heat via ionic friction…"

Comment 6. Line 86: Guidelines and literature to do not agree on a minimum or maximum size for treatment of symptomatic benign thyroid nodules and smaller nodules in a thin patient depending on location will also be candidates for treatment. Would change wording to suggest nodules larger than 20 – 30 mm are the ones most likely to cause symptoms. Would also mention that cosmetic problems and autonomously functioning nodules are also considered indications for RFA of benign nodules. It is noted that autonomously functioning nodules are mentioned later in the review so they do not specifically need to be mentioned here depending on authors preference.

Reply 6: Thank you for this important clarification. Lines 41-43 have been revised as follows: "RFA is indicated for patients with benign nodules causing compressive or cosmetic concerns, which, depending on location and patient habitus, are generally greater than 20mm-30mm in size.[9–11]"

We chose not to mention AFTN in this specific part of the introduction since there is a separate section addressing these lesions.

Comment 7. Line 87 – 88: Please note that the reference is a consensus statement (lower burden of literature review and evidence) rather than a guideline. Would state as such.

Reply 7: Thank you, this has been revised as follows: ". Consensus recommends against treating asymptomatic nodules, regardless of size.[8]"

Comment 8. Line 89: Two benign FNA biopsies are generally considered standard of care however opinions vary as to whether one core biopsy is enough.

Reply 8: Thank you for this comment, and we agree the literature surrounding CNB is variable. To reduce confusion, this mention has been removed.

Comment 9. Line 92: Please mention that goal of therapy is amelioration of symptoms or cosmetic problems rather than specific volume reduction – generally a volume reduction of 50% is associated with improvement in symptoms/cosmesis which is why this value has been arbitrarily designated procedural success in most of the literature.

Reply 9: Thank you for highlighting this. The text has been revised as follows: "Volume reduction of 50% is considered a procedural success, as it is often sufficient to relieve compressive symptoms and cosmetic concerns."

Comment 10. Line 92 – 93: Please mention the range of volume reduction achieved in the literature and include only primary literature in the references (reference 11 is a review article). Would preferably also include US experience.

Reply 10: Ranges have been included and the review reference removed. The text has been revised as follows: "Average volume reduction between 67 and 81% at 12 months are reported after a single session of RFA.[12–14]"

Comment 11. Line 99 – 100: Please give reference.

Reply 11: This sentence is now cited in the text.

Comment 12. Line 106 – 107: Please note that RFA can be performed on multiple nodules in the same patient if they meet criteria so would rewrite this to focus on RFA being a valuable option for patients with symptomatic nodules and those causing cosmetic problems.

Reply 12: Thank you for pointing this out. We have revised the text as follows: "Overall, RFA is increasingly recognized as a valuable option for the patient with symptomatic or cosmetically bothersome benign thyroid nodules."

Comment 13. Line 119: Please write out radioactive iodine or indicate RAI is the abbreviation earlier in the article, i.e., line 112.

Reply 13: Thank you. This has been written out in its first use.

Comment 14. Line 118 – 119: Please provide references.

Reply 14: This sentence was intended only as an introduction to lead into discussion of the subsequent article by Happel et al, so we did not feel it necessitated a separate citation.

Comment 15. Line 119 – 121: Please note that the quoted study combines laser ablation (rather than RFA) with RAI ablation, and as such would not be applicable to this review.

Reply 15: Thank you very much for bringing this to our attention. The study by Happel et al is instead discussed, which looks at combination RFA and RAI. The text has been revised as follows: "Happel et al reported a series of 15 patients receiving combination RFA and RAI.[29] Volume reduction in this group was significantly improved compared with the RAI only group, and euthyroidism was achieved in all patients.[29] Unpublished data from this same group suggests combination therapy may also require lower I^{131} doses."

Comment 16. Line 155: Please add "in greatest diameter" or give volume of recurrent lesions.

Reply 16: "In greatest diameter" has been added to this sentence.

Comment 17. Line 156: "reported a mean volume reduction of 99.5% and complete disappearance of 93.1% of lesions after 80 months of follow-up."

Reply 17: This has been revised as suggested.

Comment 18. Line 168: Wouldn't call it a proliferation given that there are a very limited number of studies.

Reply 18: This now instead reads "There is increasing literature available regarding the efficacy and safety of RFA in treating papillary thyroid microcarcinoma (PTMC)."

Comment 19. Line 172: Please delete "a number of" unless more than 3 – 5 studies are to be referenced.

Reply 19: This has been deleted.

Comment 20. Line 173: Please delete "in a number of studies"

Reply 20: This has been deleted.

Comment 21. Line 183: “Volume reduction of near 100% was achieved at two years”

Reply 21: This has been revised as suggested in line 223.

Comment 22. Line 197 – 198: “RFA may have a legitimate place”

Reply 22: This has been revised as suggested in line 243.