Peer Review File

Article information: https://dx.doi.org/10.21037/gs-23-18

Reviewer A

Good review regarding indications and Guidelines for RFA. All recent relevant studies were cited in your review. No more improvements needed before publication

Reviewer B

This is an excellent review of current indications for RFA for thyroid nodules, both benign and malignant. There are some areas where the impact of this review might be increased.

Comment 1: *Though the review is limited to RFA, you mention one study of thermal ablation (lines 129-130) where microwave ablation was the other technique used. it would be helpful in the Introduction to mention that RFA is a type of thermal ablation (including microwave and laser) and at least acknowledge these other techniques with perhaps any relevant reference to their effectiveness, though it is accepted that there is much more evidence associated with RFA.*
Reply 1: Thank you, this has been addressed. We now acknowledge both chemical and thermal ablative techniques in the introduction and highlight that RFA and laser ablation is the most thoroughly studied in lines 146-163

Comment 2: *In the Technique section, you mention ablation zones (lines 90-99). A simple description of how these are defined (whether by expected temperature rise or some other parameter) and whether there is standardisation of the definition of ablation zones across studies, would be helpful to the reader unfamiliar with the practicalities of the technique.*
Reply 2: Thank you, this has been addressed in lines 201-204 talking about transient hyperechoic changes on US.

Comment 3: *In the section on Primary Malignant Disease (line 167), the focus is on proven carcinomas less than 1cm diameter. Is there any evidence for a role in cancers larger than this, given than in Recurrent Malignant Disease, you regard up to 2cm as being appropriate (line 225)?*
Reply 3: There remains little data on RFA use on papillary macrocarcinomas (>1cm) let alone 2cm. There is a statement by Orloff et al saying that if the tumor size is causing compressive symptoms, then RFA may be of value. This is incorporated in the manuscript in lines 357-361

Comment 4:
A few minor points:
Comment 4A: *The statements in lines 64-66 and 75-77 need references added. –*
Reply 4A: This is added on line 134
Comment 4B: *Line 222: "who are not amenable"*
Reply 4B: This is added on line 423
Comment 4C: *Line 226: "who decline or are unable to tolerate surgery" –*
Reply 4C: Changed in line 423
Comment 4D: *Reference 7 is incomplete –*
Reply 4D: This is now complete

Reviewer C

Comment 1: *Given the title of the paper, expect the abstract to include the criteria for selection of the guidelines reviewed, and some details regarding what sources were looked at.*
Reply 1: Thank you, a quick line about sources used in included in the abstract lines 82-85

Comment 2: *Line 67: It would be pertinent to mention what percentage of thyroid surgeries are performed by high-volume surgeons as opposed to low-volume surgeons as the complication rates differ. The complication rate of a very high-volume surgeon may be very low (lower than RFA) however the majority of thyroidectomies in the US are not performed by high-volume surgeons.*
Reply 2: Thank you, this important point regarding that the majority of thyroidectomies are being done by low-volume surgeons has been incorporated in the introduction in lines 140-143

Comment 3: *Line 76: Most physicians perform RFA with only local anesthesia and no sedation.*
Reply 3: Thank you, this has been changed in line 165

Comment 4: *Line 86 – 87: Would include a paragraph on how these "guidelines" were selected i.e. inclusion criteria, exclusion criteria, search methodology etc. Specifically, how many are "guidelines" i.e. based on a robust review of the literature and methodology with recommendations given based on the strength of evidence versus consensus statements given mainly based on "expert opinion" without a detailed and thorough review of the literature included. Would indicate that these are summarized in a table at this point instead of abruptly going into a description of the technique.*
Reply 4: Thank you, this has been including in a new "methods" section. Lines 179-196

Comment 5: *Line 105: Would give typical size range and volume of nodules that are symptomatic (with reference).*
Reply 5: This is hard to clearly define. Symptomatic nodules are typically subjective. While there have been efforts to standardize symptomatic complaints using a scoring system to help with follow-up, there is unlikely to be a "size threshold" for a thyroid nodule to become symptomatic. This would also depend on the patients' body habitus.

Comment 6: *Line 161 – 162: The normalization of TSH is related to volume reduction – with an approximate volume reduction of at least 75 – 80% required to achieve euthyroidism in 50% of patients as indicated in the Bernardi, et al and Cesario, et al study; with higher likelihood of euthyroidism when volume reduction is > 80%. Since smaller nodules respond better to RFA i.e. have greater volume reduction, they are more likely to have > 80% volume reduction and thus a higher chance of euthyroidism. Smaller volumes responding better is replicated in US studies as well, Hussain, et al – 75% euthyroidism in autonomously functioning thyroid nodules, smaller responding better, median initial volume ~ 5.4 ml (< 12 ml as noted in Cesareo, et al. Would also mention a more complete ablation would be required to achieve "success: in case of AFTN.*

Reply 6: Thank you for this comment. We revised the manuscript to include the concept that smaller nodules will have greater volume reduction and may be the reason why patients will have euthyroidism (lines 331-335) However, it is important to state that while the work by

Bernardi et al strongly suggest such a theory with a volume reduction rate of 81% vs 68% in those that achieved versus did not achieve euthyroidism, but it did not reach statistical significance (p=0.08). Similarly, a meta analysis also did not find a correlation.

Comment 7: *Line 169 – 170: Given that current guidelines do not recommend biopsying nodules less than 1 cm in size even if they have suspicious features (unless there is some pressing need to do so such as location) it would be interesting to comment on how often this is happening and why. The data for successful application of RFA is fairly strong in microPTC – although I wonder why so many would be diagnosed. Perhaps a difference in various international guidelines for biopsying thyroid nodules will put this in perspective.*
Reply 7: Thank you for your comment. We agree it is very interesting why so many microcarcinomas are being identified. Surely a reason for over identification of thyroid nodules is the abundance and relative ease of imaging in resource abundant countries. However, going over the different indications/practices of thyroid nodule work-up is out of the scope of this paper.

Comment 8: *Line 195: Would specify which international consensus statement.*
Reply 8: Thank you this has been clarified in line 424

Reviewer D
This review on the possibilities of treating benign and malignant thyroid nodules by radiofrequency ablation is well written in terms of content and also didactically well structured. In some places, the text needs to be clarified or supplemented and, above all, the numerous grammatical errors, which are conspicuous even for a non-native speaker, need to be revised.

Comment 1: *Title: The term "thyroid" should definitely be included somewhere in the title, as the review refers exclusively to this organ.*
Reply 1: Thank you, this has been addressed in the title

Comment 2A: *Line 45: who will simply refuse*
Reply 2A: This paragraph has been revised and no longer in the manuscript
Comment 2B: *Line 48: I believe that based on the existing literature and the numerous guidelines, the word "potential" could be easily deleted.*
Reply 2B: this has been delete in line 71
Comment 2C: *Line 55: to standardize indications*
Reply 2C: addressed in line 174

Comment 3: *Line 64-66: "Total thyroidectomy or thyroid lobectomy continues to be the gold standard for definitive management of symptomatic and malignant thyroid nodules". - here I would add something like: "... whereas it would be more precise to further differentiate between "solid" and "predominantly cystic" or "cystic" nodules, as mainly the latter are an excellent and rewarding indication for thermoablation.*
Reply 3: Thank you for your comment. We agree that differentiating solid vs cystic nodules will help the reader better understand the nuance of thyroid nodule management. In the referenced lines, we were primarily talking about surgical management and later transition it to

chemical/thermal ablation. We briefly describe chemical/thermal ablation and how the formal is better for cystic/predominately cystic nodules while thermal ablation is effective for solid nodules in lines 146-163

Comment 4: *Line 76: "sedation" - this statement is not valid for the vast majority of thermoablation-centers, as these only perform local anaesthesia, but not sedation. Please rephrase.*
Reply 4: Thank you, this has been addressed in line 165

Comment 5: *Line 83: there*
Reply 5: Thank you, this has been addressed in line 172

Comment 6: *Line 92-94: This reviewer is unclear about the italicized part of the sentence:: One limitation to this technique was that thyroid nodules were frequently ellipsoid, and that the close proximity to other important cervical structures prohibited indiscriminate ablation margins. – did you mean something like: "precluded fully ablated nodular margins" (?)*
Reply 6: Thank you, your interpretation is correct, it is corrected on lines 204-207

Comment 7: *Line 95: delete "were"*
Reply 7: addressed in line 208

Comment 8: *Line 96: a technique that "conceptually" divided the nodule (this seems important)*
Reply 8: addressed in line 209

Comment 9: Line 97: reformulate this line please
Reply 9: Thank you, this has been reworded on lines 209-223

Comment 10: *Line 105: delete "to" grow –*
Reply 10: addressed in line 231

Comment 11: *Line 114-118: These lines convey that a "second" RFA has no advantage over a "one-time" procedure. However, it must be mentioned that in the cited study the second procedure was performed only one month after the first intervention. If, for example, one had waited a year until the volume regression was almost complete and then performed a second RFA, the result would have been significantly different. The timing of the two procedures must therefore be seen as a critical and important limitation and should be mentioned in the text.*
Reply 11: Thank you, this has been clarified with an additional reference in lines 259-262

Comment 12: *Line 118-120: this is not a logical sequence within the sentence, please rephrase. A few sentences on the occurrence of "recurrences" should definitely be included here, the reference to the fact that the results are "durable" is too little here.*
Reply 12: Thank you, this has been rephrased. Additionally, we included the recurrence rates that was reported at the 2-, 4- and 5-year follow-up in lines 273-278

Comment 13: *Line 134: published guidelines*
Reply 13: addressed in 303

Comment 14: *Line 143-146: Two important pieces of information are missing here to better understand this sentence: first, the data refer to a 1-year observation period only (recurrences in autonomous adenomas occur later and not infrequently) and second, that all patients were given a "fixed" and relatively high dose of RI (15 mCi).*
Reply 14: Thank you, these two pieces of information has been added to the sentence on lines 312 and 316

Comment 15: *Line 146: However, other "studies" ...*
Reply 15: addressed in line 318

Comment 16: *Line 147-148: The Korean literature suggests that….*
Reply 16: addressed in line 319

Comment 17: *Line 150: "only" 45-80% had inactive nodules.*
Reply 17: addressed in line 321

Comment 18: *Line 155: suggestion: the incomplete ablation of the "nodule margins"*
Reply 18: addressed in lines 326-327

Comment 19: *Line 163: therapies*
Reply 19: addressed in line 352

Comment 20: *Line 172: the work "has" shown…*
Reply 20: addressed in line 365

Comment 21: *Line 174: high grade "suspicious" features…*
Reply 22: addressed line 367

Comment 22: *Line 222: WDTC who "are" not amenable…*
Reply 22: addressed in line 423

Comment 23: *Line 223: also "highlighted" ...*
Reply 23: addressed in line 424

Comment 24: *Line 235: refuse or "are" unable…*
Reply 24: addressed in line 444