

Peer Review File

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Review Comments (Round 1)

Reviewer A

This is an interesting paper summarizing the available evidence about side-effects and complications from radio-frequency ablation.

Comment 1: The Introduction would benefit from being a bit more expansive, particularly around the indications and use of RFA. You cite a systematic review of RFA use (line 91, ref 7), it would be helpful to understand what the range of indications for RFA were in those 2786 nodules. There are many different types of nodules and with a range of different sizes and understanding whether these features relate to individual complications would be helpful.

Reply 1: Thank you for your comment, we have modified the text as advised.

Changes in the text: Please see changes in paragraph “Overall” under “Main Body” of the manuscript (page 5).

Comment 2: You mention a “linear dose relationship” between radiation and cancer incidence (line 73). This is a complex area: although higher doses are linearly related to cancer risk, these are multiple doses given for thyroid cancer, and it is uncertain whether the relationship remains linear at low single doses used for benign disease.

Reply 2: Thank you for your comment, this sentence has been reworded for clarity.

Changes in the text: Please see changes in the first paragraph under “Introduction”

Comment 3: Surgical management (line 77) for thyroid nodules should be referenced.

Reply 3: Reference added

Changes in the text: Please see the first paragraph under “Introduction”

Comment 4: As this is basically a list of adverse effects with information about their incidence and timing, it would read better if the list was ordered more logically – for example, grouping immediate effects (pain, fever, hypertension etc.), endocrine effects, nerve injury etc. I would suggest using just one decimal place for all the % incidence

values.

Reply 4: Thank you for your comment, we have updated the manuscript into groupings of nerve injury, immediate effects, endocrine effects, iatrogenic injury, and other. We appreciate the comment regarding the one decimal place, but we'd gently prefer to cite our sources as accurately as possible and accordingly keep incidence rates reported to two decimal places. We hope this is fine.

Changes in the text: Groupings are in bold and italicized throughout the main body of the text.

Comment 5: In line 96, you describe recurrent laryngeal palsy as “a relatively common” major complication but go on to say this occurs in approximately 1%. Is this what you mean here? For nerve injuries it would be helpful to understand the relative proportion of whether these are temporary versus permanent (lines 103-107). The commonest strategy during surgery to avoid nerve damage is to use a nerve monitor. This should be given appropriate mention in lines 113-118.

Reply 5: Thank you for your comment, we have adjusted the wording in your line 96 by deleting “relatively common.” The study cited by Mazzeo et al. referenced in your lines 103-107 has been clarified as this was a permanent nerve injury. A sentence was added discussing the use of intraoperative nerve monitoring.

Changes in the text: Please see the paragraphs under “Recurrent Laryngeal Nerve Palsy” in the “Main Body” text.

Comment 6: With such a lot of data, the presentation might be improved by having a table for some of the complications and presenting pooled data.

Reply 6: Good thinking, we strongly agree. We have now provided a table reporting the incidence rate of these complications.

Changes in the text: Added the table below.

Table 1. Complications following RFA and their reported incidence rates.

Complication	Incidence Rate
Transient Recurrent Laryngeal Nerve Palsy	0.86% – 1.02%
Permanent Recurrent Laryngeal Nerve Palsy	0.00%
Brachial Plexus Injury	0.07%
Horner Syndrome	0.13%

Nodule Rupture	0.19% – 2.5%
Hematoma	0.9% – 2.1%
Hypertension	0.46%
Vasovagal Reaction	0.34%
Fever	0.3% – 6.0%
Skin Burn	0.27%
Edema	1.00%
Pain	0.8% – 15.7%
Vomiting / Nausea	0.62%
Permanent Hypothyroidism	0.07%
Cough	1.26%

Reviewer B

Comment 7: Line 68: Would clarify that anti-thyroid medications and RAI only apply to non-functional thyroid nodules.

Reply 7: Thank you, this was adjusted.

Changes in the text: Please see the beginning of the “Introduction.”

Comment 8: Line 70 – 71: RAI is not the ideal treatment for cosmetic and compressive symptoms as it does not cause significant volume reduction. It would be palliative at most – when surgery is not an option.

Reply 8: Thank you for your comment, this sentence has been restructured to describe the broad indications for RAI per ATA guidelines: remanent ablation, adjuvant treatment, treatment of a known disease.

Changes in the text: Please see the first paragraph of “Introduction.”

Comment 9: Line 83: Would use the term “electrode” per standard reported guidelines rather than catheter.

Reply 9: Thank you, this has been accordingly addressed.

Changes in the text: Please see the second paragraph of “Introduction.”

Comment 10: Line 91: Wouldn’t call it recent – it’s from 2017, though it is noted that no significant meta-analysis has been performed after this.

Reply 10: This sentence has been adjusted for clarification to say, “most recent, comprehensive meta-analysis.”

Changes in the text: Please see the first paragraph of “Main Body” under “Overall.”

Comment 11: Line 98 – 100: There should be some mention of whether the size of the initial nodule has anything to do with increase risk of recurrent laryngeal nerve injuries and other complications (similar to how malignant nodules have a higher complication rate compared to benign nodules). The study by Kandil, et al has an unusually low initial volume of thyroid nodules – thus many of these are likely to be low risk nodules (not abutting critical structures in the neck on all sides).

Reply 11: Thank you for this comment. Baek et al. (2012) had no mention of nodule size and complication in their manuscript, we clarified the correlation between the location of nodule (close to the recurrent laryngeal nerve) and nerve injury.

Changes in the text: Changes are noted in the first paragraph under “Recurrent Laryngeal Nerve Palsy.”

Comment 12: Line 111: Would use the term “operator” or “practitioner” instead of surgeons – it’s a non-surgical technique.

Reply 12: This has been adjusted to “practitioner.”

Changes in the text: Please see the changes noted in the second paragraph under “Recurrent Laryngeal Nerve Palsy.”

Comment 13:

Line 115: You can’t inject saline for hydrodissection in RFA (only in laser or MWA) because it transmits current so it would have to be D5W.

Reply 13: Thank you, this has been updated.

Changes in the text: Please see the changes noted in the second paragraph under “Recurrent Laryngeal Nerve Palsy.”

Comment 14:

Line 116 – 117: If the “moving shot” technique is to be described as “ablating in conceptual units” then this will need to be described more fully.

Reply 14: This sentence has been reworded for further clarification.

Changes in the text: Please see the changes noted in the second paragraph under

“Recurrent Laryngeal Nerve Palsy.”

Comment 15:

Line 117 – 118: Please describe the frequency of such conversations. And would note that talking to the patient is recommended for continuous voice assessment during the procedure and this does allow for feedback i.e. not just “may allow”. This is the main reason the procedure is performed under local anesthesia rather than general.

Reply 15: Thank you very much for this insight and clarification, we have adjusted this sentence as suggested.

Changes in the text: Please see the changes noted in the second paragraph under “Recurrent Laryngeal Nerve Palsy.”

Comment 16:

Line 119: Would also mention “rescue hydrodissection” as an important mitigation strategy in case of thermal injury to the nerve (Aljammal, et al, Lee, et al, and Chung et al).

Reply 16: This was mentioned as a strategy, but clarification was added to include the full name “rescue hydrodissection.”

Changes in the text: Please see the changes noted in the second paragraph under “Recurrent Laryngeal Nerve Palsy.”

Comment 17: Line: 122: It’s more so the extravasation of the nodule through the thyroid capsule rather than just leakage of extrathyroidal fluids – please describe in more detail.

Reply 17: This sentence was corrected, and more information on nodule rupture is discussed in this paragraph.

Changes in the text: Please see the changes noted in the first paragraph under “Nodule Rupture.”

Comment 18:

Line 123/nodule rupture: Please give details of when it would require more invasive methods of treatment, and what the criteria would be. How long should conservative measures be attempted before attempting to drain or surgically remove? How would it be assessed for infection, etc.

Reply 18: Yes, this should be touched on, thank you. Conservative management such a course of antibiotics may be appropriate for smaller nodules. Surgical intervention is indicated when a thyroid abscess is detected, even if a small nodule.

Changes in the text: Please see the changes noted in the first paragraph under “Nodule Rupture.”

Comment 19:

Line 127 – 128: It is not so much that anterior nodules tend to rupture but rather that nodules most commonly rupture through the anterior part of the thyroid capsule.

Reply 19: Thank you for your insight, this sentence has been clarified.

Changes in the text: Please see the changes noted in the first paragraph under “Nodule Rupture.”

Comment 20:

Line 129: It is thought to be because of delayed bleeding – although I don’t believe that this has been confirmed.

Reply 20: Thank you for your insight, this sentence has been clarified.

Changes in the text: Please see the changes noted in the first paragraph under “Nodule Rupture.”

Comment 21:

Line 135: ... initially greater than 4.5 cm in diameter

Reply 21: Great catch, thank you, this has been adjusted.

Changes in the text: Please see the changes noted in the first paragraph under “Nodule Rupture.”

Comment 22:

Line 168: Would write “conjunctival redness” instead of conjunctival complaint.

Reply 22: This has been adjusted, thank you.

Changes in the text: Please see the paragraph under Horner syndrome.

Comment 23:

Line 193 – 194: I wouldn't suggest giving levothyroxine as a way of mitigating the complication – rather treating the complication. At this point, it's not even clear if hypothyroidism is a complication. The transient thyroid dysfunction is likely thyroiditis. And TPO Ab place patients at increased risk of hypothyroidism compared to the general population – this doesn't specifically have anything to do with the RFA procedure and is likely unrelated. The only reason to check these pre-procedure would be to identify patients who are higher risk of hypothyroidism so as to counsel them that they may develop hypothyroidism with time regardless of whether or not they get the RFA procedure.

Reply 23: Thank you for this insight, we greatly appreciate your insight. We have adjusted the sentence as suggested.

Changes in the text: Please see the last sentence in the paragraph under Hypothyroidism.

Comment 24:

Line 202: Is there a specific blood pressure above which the procedure should not be performed? Should the blood pressure be continuously checked during the procedure? Should it just be checked before the procedure starts? Would be more specific and detailed. Different practitioners are likely to have differing opinions regarding this – many do not use continuous blood pressure monitoring during the procedure.

Reply 24: Thank you for this comment. The Korean guidelines actually recommend continuous blood pressure monitoring, though I am not sure how widely exercised this is. At our practice, this is not done, and neither is performed by close colleagues of mine. Patients with hypertensive urgency should likely not be treated by RFA until their blood pressure has been adequately treated.

Changes in the text: Please see the last sentence in the paragraph under Hypertension.

Comment 25:

Line 207 – 208: This is actually fairly rare to the point of being the rare case report in cases of FNA. It may actually be more common in RFA of malignant lesions. Please cite more references to make your point here.

Reply 25: References have been added and the sentence clarified, thank you.

Changes in the text: Please see the paragraph under “Needle tract seeding.”

Comment 26:

Line 227: Since the parathyroid adenoma was intra-thyroidal the patient probably had a hemi-thyroidectomy rather than just a parathyroidectomy? Interesting that it grew rather than getting smaller as RFA is actually a good way of treating an intra-thyroidal parathyroid adenoma – presumably the blood supply was not ablated/and the nodule was not completely ablated as it was treated like a benign thyroid nodule.

Reply 26: Yes, this was a very interesting case. We checked and the patient did receive a L parathyroidectomy instead of a hemithyroidectomy. Thank you for your insight.

Changes in the text: none

Comment 27:

Line 242: Please give details on how to treat.

Reply 27: Thank you for this comment. This has been reported in only a single patient, and they were adequately treated with oral methylprednisolone

Changes in the text: We have updated the text. Please see the last line in the header Pseudocystic Transformation.

Comment 28:

Line 282 – 284: Also methimazole doesn't actually treat the hyperthyroidism from thyroiditis (leakage of pre-formed thyroid hormone into bloodstream after inflammation) – it does prevent the thyroid from making more thyroid hormone which is not the problem in most cases.

Reply 28: Thank you, this was clarified.

Changes in the text: Please see the paragraph under “Transient Thyrotoxicosis”

Comment 29:

Line 305: Would differentiate between severe pain that is lasting for days and mild transient pain during the procedure. Some amount of discomfort is expected and should be counted as a side effect rather than a complication.

A table summarizing the most common complications and mitigation strategies would be useful.

As would a summary discussion describing which of the complications are most

common. Tracheal and esophageal injury have not been mentioned. One patient in a clinical trial for RFA of metastatic lymph nodes has also died after RFA complications. The differences in complication rates between benign and malignant lesions need to be stated more clearly. There also needs to be some comparison with the complication rates of other thermal ablation procedures and surgery.

Reply 29: We adjusted this section to just “Pain and/or heat,” to account for both transient and longer-lasting pain. We focus on intolerable, longer-lasting pain as a complication rather than the expected side effect. We have now provided a table reporting the incidence rate of these complications. We gently thought it best for our readers to read the respective section header to best understand the prevention/mitigation/treatment strategies, as it would better inform the surgeons performing RFA as well as allow a clean / presentable table. We hope this is agreeable with the reviewer. We have also added a section for Tracheal / Esophageal injury – thank you for this. We have added a paragraph at the end for the differences in benign and malignant treatment and their complication rates as well. We have also added a paragraph discussing laser and microwave ablation.

Changes in the text: Please note the section titled “Pain and or heat.” We have now provided a table reporting the incidence rate of these complications. See below. We have also added a section for Tracheal / Esophageal injury – thank you for this. We have added a paragraph at the end for the differences in benign and malignant treatment and their complication rates as well. We have also added a paragraph discussing laser and microwave ablation.

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Skin Burn	0.27%
Edema	1.00%
Pain	0.8% – 15.7%
Vomiting / Nausea	0.62%
Permanent Hypothyroidism	0.07%
Cough	1.26%

Review Comments (Round 2)

Reviewer A

Comment 1: Thank you. I have now read through the authors' revised manuscript. This reads very well and is much clearer than the original version.

Reply 1: Thank you.

Comment 2: I would though suggest some rearrangement on some of the sections. Following line 174 "Immediate effects", the first section is Nodule Rupture (line 175) which is described as occurring "months after RFA" (line 182), so not really immediate whereas Hypertension (line 209) and Vasovagal Reaction (line 230) are. Also the sections on Hematoma (line 197) and Diffuse glandular hemorrhage (line 200) would be better placed in adjacent sections. It would perhaps be better to list the immediate effects first, before the sections on nerve injury, though in some sense, these might also be classed as immediate. Either way, a little re-ordering would seem appropriate.

Reply 2: Thank you for this comment, the authors agree. We have accordingly re-ordered the work, though we preferred to maintain 'nerve injury' and its contents (RLN paresis/palsy, brachial plexus injury, Horner Syndrome) first – as we think this to be the most important (and most common) complication. We have moved 'nodule rupture' and 'edema' sub-headings to the 'other' heading as these are more delayed effects as you mention. We have also ensured that 'hypertension', 'diffuse glandular hemorrhage', and 'hematoma' are reported and discussed consecutively.