

Peer Review File

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Reviewer A

Comment 1: This appears as invited editorial on the subject of NIRAF for parathyroid gland identification during thyroid surgery. This appears as an invited editorial by the journal. The manuscript is appropriate if it is an invited editorial. However, it adds no new information to the existing literature. It is a good summary of the recent advances in parathyroid identification during thyroid surgery.

Reply 1: No changes were made to the text.

Changes in the text: N/A

Reviewer B

Comment 2: This review deal with current cutting edge technology for saving parathyroid glands. I think this article is good introduction to many endocrine surgeons who want to start the fluorescence guided thyroid surgery. Thank you for your effort.

Reply 2: No changes were made to the text.

Changes in the text: N/A

Reviewer C

Comment 3: The article is well-structured and presents an important discussion for the use of NIRAF + ICGA in thyroid surgery. Attention to minor grammatical details
Overall, this comment brings a significant contribution to the ongoing research on improving thyroid surgery outcomes. Addressing the grammatical issues will strengthen the manuscript and its impact on the scientific community.

Reply 3: Multiple minor grammatical errors corrected.

Changes in the text:

1. Text corrected to “most patients” – line 13.
2. Formatting of NIRAF + ICGA (compared to NIRAF+ICGA) has been standardized throughout text.

Reviewer D

Comment 4: You have performed a very rich invited editorial commenting on Di Lorenzo et al paper. Most of your commentaries are well centered with relevant literature basis. Although on lines 68-69 you have attested that: "NIRAF is likely most beneficial for surgeons who are less experienced or who perform a smaller volume of thyroid surgeries." and don't cite where this data come from. It's important to remember that in the 2000's during nerve monitoring adoption we all thought it would be most beneficial for less experienced or low volume surgeons. On the contrary, Sturgeon et al (1) have shown that high volume surgeons were more likely to adopt this new technology, perhaps because they have experienced more complications than low volume surgeons, so they were more likely to change their practice to avoid complications. You should mention that it can also happen with fluorescence adoption for parathyroid preservation rather than attest that only less experienced and low volume surgeons will use it. I would kindly suggest that you reformulate it, or on your own judgment, use this reference to change your statement. On cost analysis you should also mention that although nowadays the cost is high, a broad adoption would make it cheaper and easier to its utilization, as happened with other technologies such as nerve monitoring, advanced energy and robotic surgery.

1. Sturgeon C, Sturgeon T, Angelos P. Neuromonitoring in thyroid surgery: attitudes, usage patterns, and predictors of use among endocrine surgeons. *World J Surg.* 2009 Mar;33(3):417-25.

Reply 4: Wording of statement changed to be more theoretical. New reference added with mention that high volume surgeons were more likely to adopt new technology in the past.

Changes in the text: Line 62 Text changed to "Theoretically, NIRAF would be most beneficial". Line 63 text changed to "but this population may be less willing". Lines 65-68 text added to mention low volume surgeons were less likely to adopt new technology.

Reviewer E

Comment 5: It reads as a good summary of the current evidence around the use of near-infrared fluorescence imaging and indocyanine green fluorescence for parathyroid preservation during thyroidectomy.

A few minor suggestions:

Page 1, line 8 - Invited Editorial - should Editorial

Page 1, line 26 - suggest comma after 2013 so it would read "In 2013, Mcwade et al"

Page 3, line 57 - I think you mean temporary HYPOparathyroidism rather than hyper?

Page 4, line 79 - DiLorenzo should have a space (Di Lorenzo)

And the editorial team may correct me if wrong depending on the journal referencing style, but normally when using et al within the text, I don't think there should be a comma between the name and et al.

I.e. "Di Lorenzo et al" "Rossi et al" rather than "Di Lorenzo, et al" as you have written

Reply 5: Minor grammatical errors corrected as suggested above. Formatting of et al changed to exclude commas.

Changes in the text:

1. Typo corrected to "editorial" -, line 4

2. Typo corrected at line 21, text now reads “In 2013, McWade et al”
3. Typo corrected to “hypoparathyroidism” at line 50
4. “et al” formatting has been standardized to exclude comma.

Reviewer F

Comment 6: I had the privilege of reviewing the invited editorial titled, "Near-Infrared Fluorescence Imaging Plus Indocyanine Green Fluorescence in Patients Undergoing a Total Thyroidectomy and Central Neck Lymph Node Dissection: Is It Worth It?" This editorial offers a well-balanced and insightful reflection on the application of NIRAF and ICGA technologies in total thyroidectomies with central neck lymph node dissection, highlighting their potential benefits and addressing important considerations. The editorial primarily focuses on the study "Impact of Near-Infrared Fluorescence Imaging Plus Indocyanine Green Fluorescence on Postoperative Hypoparathyroidism Rates After Total Thyroidectomy and Central Lymph Node Dissection" by Di Lorenzo et al., while also providing background on the clinical issues these techniques address and a brief overview of previously published data in the field.

The author effectively underscores the strengths of these techniques, emphasizing their ability to facilitate the identification of parathyroid glands and their blood supply. The data presented demonstrate that these methods are superior to visual identification alone, which is crucial since the number of parathyroid glands preserved in situ is a significant predictor of permanent hypoparathyroidism. Furthermore, as noted by the author, NIRAF and ICGA have been shown to reduce transient hypoparathyroidism, as evidenced by the study by Di Lorenzo et al. and two randomized trials mentioned in the text.

Additionally, the author discusses the challenges associated with NIRAF and ICGA. The cost-benefit analysis is particularly difficult, especially when managing temporary hypoparathyroidism with affordable treatments. Moreover, there is insufficient data proving that NIRAF significantly reduces permanent hypoparathyroidism, which complicates its justification for broader use. However, the potential benefits of these techniques might be most pronounced among low-volume surgeons.

In conclusion, this nicely written editorial provides an analysis of NIRAF and ICGA technologies, exploring their potential benefits, and addressing pertinent clinical considerations. I believe this editorial would add value for Gland Surgery and its readers.

Reply 6: No changes were made to the text.

Changes in the text: N/A

Reviewer G

Comment 7: Overall, a very well written editorial. The authors identify many of the key concepts and highlight some of the salient papers to date.

I suggest adding a mention of how postoperative hypoparathyroidism was defined in the Di Lorenzo paper reviewed. In the same vein it would be helpful to highlight that some of the challenges in showing benefit of this technology lies in the variability of how temporary and permanent hypoparathyroidism are defined and measured as well as the overall low incidence and therefore number needed to treat to show benefit.

Lastly, I would suggest adding some mention of the learning curve to using technology properly. As with any surgical technology, this reality favors the high-volume surgeon and remains something to keep in mind for those looking to adopt this technology.

Reply 7: Definitions of how postoperative hypoparathyroidism was defined in the Di Lorenzo et al paper were added. Mention of high learning curve which may dissuade lower volume surgeons was added to the text.

Changes in the text: Line 37, “(less than six months)” added. Line 39, “(lasting over six months)” added. Line 67 text added mentioning the high learning curve of NIRAF technology.

Reviewer H

Comment 8: It provides a summary of autofluorescence and ICG observation of parathyroid glands and cost-effectiveness.

There is a discrepancy because the authors' title is 'in patients undergoing a total thyroidectomy and central neck lymph node dissection', but the cited article is not only malignant lesions; Benmiloud et al. had 15.8% malignant lesions in their patient population and Dip et al. 48.2%.

Moreover, several RCT trials were published and they should be considered in this manuscript.

Bergenfelz A, Barczynski M, Heie A, et al. Impact of autofluorescence for detection of parathyroid glands during thyroidectomy on postoperative parathyroid hormone levels: parallel multicentre randomized clinical trial. *Br J Surg.* 2023;110(12):1824-1833. doi:10.1093/bjs/znad278

Lykke E, Christensen A, Juhl K, et al. Effect of near infrared autofluorescence guided total thyroidectomy on postoperative hypoparathyroidism: a randomized clinical trial. *Eur Arch Otorhinolaryngol.* 2023;280(5):2593-2603. doi:10.1007/s00405-023-07867-4

Wolf HW, Runkel N, Limberger K, Nebiker CA. Near-infrared autofluorescence of the parathyroid glands during thyroidectomy for the prevention of hypoparathyroidism: a prospective randomized clinical trial. *Langenbecks Arch Surg.* 2022;407(7):3031-3038. doi:10.1007/s00423-022-02624-3

Reply 8: The title was not changed as it is specifically in reference to the Di Lorenzo et al paper that this editorial is focused on, and the Di Lorenzo study included patients who underwent total thyroidectomy and central lymph node dissection. The suggested randomized controlled trial by Bergenfelz et al was added to the manuscript.

Changes in the text: Line 56, Bergenfelz et al randomized controlled trial was mentioned and cited.

Reviewer I

Comment 9: This is a well written paper that summarizes highlights in the literature regarding a novel technology for identifying parathyroid glands nicely.

There are a few suggestions to help strengthen the paper:

1) Line 56-58 - in discussion of the Benmiloud et al paper, I believe it should read, "temporary hypoparathyroidism" instead of hyperparathyroidism.

2) Lines 67 and onward for this paragraph: this section should be a bit more robust regarding the pros and

cons for this technology. It is repeating similar arguments that other authors have made regarding this technology. How about discussing the need for complicated cases with extensive malignancy, revision cases in high volume centres where surgeons are experienced but dealing with a high risk for complications in order to cure the patient of their cancer. There are many more arguments for or against the use of this technology that have not been discussed.

Reply 9: The typo mentioned has been fixed to the intended word “hypoparathyroidism”. We agree that the editorial would benefit from a more robust pros and cons discussion. Additional examples of high-risk scenarios that would benefit from NIRAF have been added to the last paragraph.

Changes in the text: Typo corrected to “hypoparathyroidism” at line 50. Additional examples of high-risk cases added to line 77-70.

Reviewer J

Comment 10: This manuscript seems timely, covering well recent clinical application of NIRAF technology. Readers will be helped by the diligent references and reviews in this journal, well deserving publication. Some detailed addition and revision of the projected cost of NIRAF, with introduction of commercially available vendors. To mention the cost-effectiveness, cost and effect is better to be given in real numbers. This manuscript is worthy of publication, with the addition of more detail in terms of cost-effectiveness.

Reply 10: We agree that adding a real number would be more impactful. Unfortunately, there are no recent cost-benefit studies of NIRAF to cite from. We have instead added a mention that there needs to be more cost-benefit studies in order to analyze the true financial impact of NIRAD.

Changes in the text: Line 70 text added “More cost-benefit analyses are needed to investigate the financial effectiveness of NIRAF”