

## Peer Review File

**Article Information:** <https://dx.doi.org/10.21037/gs-2024-522>

### Reviewer A

This is an interesting imaging analysis study from a single institution. The authors hypothesized that digital photographs of parathyroid glands analyzed by a machine-learned RF algorithm can accurately identify parathyroid glands intraoperatively. While the authors explored an interesting problem, several underlying issues with the study design and premises should be addressed.

Introduction:

**Comment1:** Line 52: A single 25mg ICG IV vial is only around \$200 in the US, which is not prohibitively expensive.

**Reply1:** Thank you for pointing out these details and for your very valuable review comments. We have made appropriate adjustments.

**Changes in the text:** Line 47-52, Second, most intraoperative identification techniques require the input of exogenous substances into the human body. Negative developers such as nanocarbons [10] incur additional costs and are difficult to metabolize in the body. Positive developers such as indocyanine green (ICG) [11] may have the problems of low specificity and limited development time. In addition, regardless of the type of contrast agent, the development effect is easily affected by the local blood supply and scarring.

**Comment2:** Line 55: Comment on the expensive upfront capital needed for systems

that utilize near-IR and parathyroid gland autofluorescence as well as the continued cost for disposables, i.e. a camera cover (Fluobeam) or a probe (PTEye), rather than putting a nebulous amount in Yuan, which does not translate well for the broad international general audience.

**Reply2:** Thank you for your very valuable review comments. We have made appropriate adjustments.

**Changes in the text:** Line 54-57, This is a noninvasive and reproducible intraoperative identification technique for parathyroid gland surgery; however, it still requires the purchase of expensive additional equipment and proficiency in its use.

**Comment3:** Line 68 Specify what kind of thyroid surgeries. The backdrop of thyroid parenchyma in the case of Graves' vs. goiter vs. cancer are different.

**Reply3:** Thank you for your very valuable review comments. We have made appropriate adjustments.

**Changes in the text:** Line71-72, thyroid lobectomy or total thyroidectomy for benign or malignant tumors

**Comment4:** Line 69 Specify what kind of “ordinary cameras” – assuming a DSLR is used, specify effective pixels, resolution, ISO, optics, etc.

**Reply4:** Thank you for your very valuable review comments. We have made appropriate adjustments in the text.

**Changes in the text:** line 78-80, The specific information of the camera is as follows: model, Canon EOS 70D; aperture value, f/5; exposure time, 1/160 seconds; ISO, 400; focal length, 5–10 cm, and flash mode, forced.

**Comment5:** Line 90 The authors should describe what kind of texture features surgeons look for with the naked eyes and how digital photos better appreciate these digitally.

**Reply5:** Thank you for your review comments. These texture features are difficult to identify with the naked eye, but they can be extracted using image analysis techniques. There are 7 groups of 104 texture features, and we have added supplementary materials

to provide a detailed introduction. In the subsequent methodology section, we also detailed that an image can be converted into 9 color channels, extracting a total of 936 texture features of  $104 \times 9$ . These features cannot be directly recognized by the naked eye and can only be extracted through image analysis techniques.

⋮ **Supplementary Material: |Texture feature details**

- 1) First order features, 19 features;
- 2) 2D-Shape-based features, a total of 10 features;
- 3) Gray Level Co-occurrence Matrix (GLCM), a total of 24 features;
- 4) Gray Level Run Length Matrix (GLRCM), a total of 16 cases;
- 5) Gray Level Size Zone Matrix (GLSZM), with 16 features;
- 6) Gray Level Dependence Matrix (GLDM), with a total of 14 features;
- 7) Neighbouring Gray Tone Difference Matrix (NGTDM), with 5 features. There are 104 features in 7 categories mentioned above.

Each of the above 104 features were extracted from all nine channels, so the total number of features was  $9 \times 104 = 936$  features.

The explanations and categories of these features are available on the website <https://pyradiomics.readthedocs.io/en/latest/>, which details the calculation formulas and principles of all the texture features used in this study.

**Changes in the text:** Line 105-106 For the details of the texture features, please see the supplementary materials. And please also see the additional supplementary materials document.

**Comment6:** Line 161 Given that the test set of parathyroid gland pictures were all surgeon-verified (100% accuracy), an accuracy of 89.6% is not impressive or helpful, unless you assume thyroid surgeons identify parathyroids with less than 90% accuracy intraoperatively.

**Reply6:** Firstly, the parathyroid glands identified during surgery were jointly judged by three senior surgeons (with more than 10 years of thyroid surgical experience). If all surgeons believed that the indicated tissue was parathyroid, they would not submit it for pathological examination and it would be recorded as correct. If any doctor suspected that the indicated tissue was not parathyroid or other tissues might be parathyroid, small pieces were cut from all suspicious tissues and sent to pathology for diagnosis and exclusion of metastatic lymph nodes or fat.

Secondly, previously reported accidental resection rates of parathyroid gland have ranged from 8% to 19%. When other methods, such as fluorescence development technology, were initially introduced, their accuracy and sensitivity were also approximately 90%. Consequently, even though our current technology is still somewhat rudimentary, there is still potential for further optimization with the increase of data volume and improvement of methods in the future. This will enable us to provide guidance to junior surgeons without disrupting the surgical process.

**Changes in the text: None.**

**Comment7:** In summary, the authors took digital photographs of parathyroid glands and put them through a series of post-processing software programs (Image J, Pyradiomic) that relied on the nine-color channel analytics and tested them for a RF algorithm. The overall accuracy of 89.6% is not very promising, unless we assume surgeons accurately identify parathyroid glands less than 90% intraoperatively. If a RF algorithm had to distinguish digital photos of apples and oranges, it would have 99.99% accuracy. Moreover, in order to have a truly efficient and effective tool, the first step should be developing an algorithm for identifying the parathyroid gland in the backdrop of the thyroid tissue.

**Reply7:** Thank you very much for your valuable comments on this study; they are particularly helpful to our research. In response to what you said, " Moreover, in order to have a truly efficient and effective tool, the first step should be developing an algorithm for identifying the parathyroid gland in the backdrop of the thyroid tissue. " Yes, this study is based on this purpose. The photos of the parathyroid glands taken in this study, as shown in Figure A of Figure 1, were all captured in the context of thyroid tissue, specifically by shooting directly within the surgical cavity. This particular photo was included in the study after we took pictures of the suspicious tissue in the surgical cavity and subsequently determined it to be parathyroid tissue.

Finally, thank you again for your excellent review. While there are some deficiencies in this study, it is the first time image analysis technology has been used to

explore these photos, and we have found the possibility of using white light images to predict the intraoperative parathyroid gland. This has certain research significance and contributions. Although it is a preliminary study, we believe that with in-depth research involving larger sample sizes across more centers, it is promising to develop an APP that can be used in clinical practice.

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#### **Reviewer B**

**Comment1:** While the idea is interesting, the paper requires improvement in the overall language. It may be helpful to have it reviewed by english services to ensure you are stating what you mean.

**Reply1:** Thank you very much for your review comments. We have made changes to the English language: the language was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified English speaking editors at AJE Company.

**Change in the text:** All the language has been improved by AJE company and shown in the whole text.

I have listed several other suggestions to help strengthen the paper:

Introduction

**Comment2:** “symptoms such as hand and foot 35 twitching “ – may wish to refer to this in clinical/medical terms

**Reply2:** Thank you very much for your review comments. We have changed this sentence into “Tetany”.

**Change in the text: Line 34:** symptoms such as tetany [5].

**Comment3:** “exacerbate conflicts between doctors and patients” – may wish to describe this differently

**Reply3:** Thank you very much for your review comments. We have deleted this

sentence.

**Changed in the text: Line 35** These injuries pose a serious threat to patients' quality of life.

**Comment4:** Avoid using the word “mainly” repetitively, it does not add any value to the sentence

**Reply4:** Thank you very much for your review comments. This word has been deleted.

**Changed in the text:** This word has been deleted in the text

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**Comment5:** Line 45 “have a complete membrane” – what does this mean?

**Reply5:** Thank you very much for your review comments. This means: The parathyroid gland is an organ with a complete capsule.

**Change in the text:** Line 44 have a complete capsule.

**Comment6:** “This method is not suitable for junior physicians.....” – maybe just state physicians with insufficient experience and delete junior physicians

**Reply6:** Thank you very much for your review comments. We have changed this in the text.

**Change in the text:** This method is not suitable for physicians with insufficient experience.

**Comment7:** The language needs improvement overall

**Reply7:** Thank you very much for your review comments. We have made changes to the English language: the language was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified English speaking editors at AJE Company.

**Change in the text:** All the language has been improved by AJE company and shown in the whole text.

**Comment8:** Line 61 “It is hoped that by taking photographs of suspected parathyroid gland tissue during surgery, the photographs can be identified and used to infer whether

the tissue is a parathyroid gland.” This statement needs to be strengthened since it is stating the purpose of the study. Is this a radiomics study?

**Reply8:** Thank you very much for your review comments. This is not a radiomics study, but it uses radiomics technology. Generally speaking, radiomics technology is mainly used for three-dimensional images such as CT, MRI. The Pyradiomics toolkit also provides methods for analyzing two-dimensional images. We use this technology to extract texture features from parathyroid gland photos and use them for analysis and modeling.

**Change in the text:** Line 63-66 By taking photos of suspected parathyroid tissue during surgery, extracting texture features using radiomic techniques, and further establishing and validating machine learning models, it is possible to identify and infer whether the tissue is parathyroid.

## Methods

**Comment9:** Line 69 – “ordinary camera” – please describe the camera use, iPhone, etc.

Was the tissue removed from the wound and then taken OR within the wound.

The methods need to be reproducible.

**Reply9:** Thank you very much for your review comments. The photos of the parathyroid glands taken in this study, as shown in Figure A of Figure 1, were all captured in the context of thyroid tissue, specifically by shooting directly within the surgical cavity. The specific information of the camera is as follows: model: Canon EOS 70D, aperture value: f/5, exposure time: 1/160 seconds, ISO: 400, focal length: 5-10cm, flash mode: forced.

**Changes in the text:** line 76-80 The photos of the parathyroid glands taken in this study were all captured in the context of thyroid tissue, specifically by focusing directly within the surgical cavity. The specific information of the camera is as follows: model, Canon EOS 70D; aperture value, f/5; exposure time, 1/160 seconds; ISO, 400; focal length, 5–10 cm, and flash mode, forced.

**Comment10:** Line 75 “Each patient took 1-4 photos.” The patients took pictures of

their own parathyroids?

**Reply10:** Thank you very much for your review comments. We have made change to this sentence.

**Changes in the text:** line 85-86 For each surgery, one to four photos were obtained from each patient.

Results

**Comment11:** Line 161 “The test accuracy, specificity, sensitivity, and AUC of the model were 89.6%, 85.7%, 91.8%, 88.7%, and 77.5%, respectively”, there are too many numbers here that do not correspond accordingly.

**Reply11:** Thank you very much for your review comments. We have made change to this sentence.

**Changes in the text:** line 175-176 The test accuracy is 89.6%, the sensitivity is 85.7%, the specificity is 91.8%, the AUC is 88.7%, and the kappa value is 77.5%.

**Comment12:** Line 162 “Although the test results of this model are not particularly high,” this does not make sense, clarify.

**Reply12:** Thank you very much for your review comments. We have deleted this sentence and make change in the text.

**Changes in the text:** line 176-178: In addition, it was preliminarily demonstrated that the textural features of photos also contribute to the prediction of parathyroid tissue, which has certain practical value.

**Comment13:** Line 171 – what are texture features? Not clearly explained. Is this only found in photos?? It is somewhat explained further down, but it should be defined earlier.

**Reply13:** Thank you for your review comments. We have add explanation of texture



features. These texture features are difficult to identify with the naked eye, but they can be extracted using image analysis techniques, only found in photos. There are 7 groups of 104 texture features, and we have added supplementary materials to provide a detailed introduction. In the subsequent methodology section, we also detailed that an image can be converted into 9 color channels, extracting a total of 936 texture features of  $104 \times 9$ . These features cannot be directly recognized by the naked eye and can only be extracted through image analysis techniques.

**Changes in the text:** Line 105-106 The detail of the texture features please see supplementary materials. And please also see the additional supplementary materials document. And Line 184-186: The texture feature characterizes the arrangement and pattern of image signals, either in their original spatial layout or in transformed representations such as Fourier or other spectral domains.