The Accuracy of Near Infrared Autofluorescence in Identifying Parathyroid Gland During Thyroid and Parathyroid Surgery: A Meta-Analysis

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Objective: We aim to assess the accuracy of near infrared autofluorescence in identifying parathyroid gland during thyroid and parathyroid surgery.

Method: A systematic literature search was conducted by using PubMed, Embase, and the Cochrane Library electronic databases for studies that were published up to February 2021. The reference lists of the retrieved articles were also reviewed. Two authors independently assessed the methodological quality and extracted the data. A random-effects model was used to calculate the combined variable. Publication bias in these studies was evaluated with the Deeks’ funnel plots.

Result: A total of 24 studies involving 2,062 patients and 6,680 specimens were included for the meta-analysis. The overall combined sensitivity and specificity, and the area under curve of near infrared autofluorescence were 0.96, 0.96, and 0.99, respectively. Significant heterogeneities were presented (Sen: I² = 87.97%, Spe: I² = 65.38%). In the subgroup of thyroid surgery, the combined sensitivity and specificity, and the area under curve of near infrared autofluorescence was 0.98, 0.99, and 0.99, respectively, and the heterogeneities were moderate (Sen: I² = 59.71%, Spe: I² = 67.65%).

Conclusion: Near infrared autofluorescence is an excellent indicator for identifying parathyroid gland during thyroid and parathyroid surgery.

Keywords: near infrared, autofluorescence, parathyroid gland, surgery, meta-analysis
INTRODUCTION

During thyroid and parathyroid surgery, identification of the parathyroid gland (PG) always relies on the visual judgment and experience of the surgeon (1, 2). Failure to identify the normal PG during thyroid surgery might result in PG damage, devascularization, and inadvertent resection, and thus bring about postoperative hypoparathyroidism. Hypoparathyroidism can lead to poor experience, prolonged hospitalization, and lower quality of life (3–5). On the other hand, failure to identify the abnormal PG during parathyroid surgery for hyperparathyroidism would result in reoperation (6, 7).

In recent decades, several tracers have been reported to assist to identify PG, but they have some disadvantages, such as lack of direct evidence, limitation of instrument and/or invasion (8–10). Indocyanine green angiography was also used to evaluated the function of PG and showed a satisfactory ability to reduce the rate of hypoparathyroidism after thyroid surgery (11–13). The near infrared autofluorescence (NIRAF), a noninvasive, label-free and rapid indicator, was introduced to intraoperatively identify PG during past years (14–17). The NIRAF of PG was first reported by Paras and his colleagues in 2011 and they found that the fluorescence intensity of PG was greater than that of the thyroid and all other tissues in the neck (18). Since then, the number of studies exploring the potential of NIRAF to identify PG during surgery has been increased and the instruments to measure NIRAF were also various (19–21). Some studies suggested that the use of NIRAF improved the early postoperative hypocalcemia rate and increase parathyroid preservation after total thyroidectomy (22, 23). However, the sensitivity of NIRAF was 81%–100% and the specificity ranged from 80% to 100% (14–16). Due to the large variety, we conduct a meta-analysis to assess the accuracy of NIRAF in identifying PG during thyroid and parathyroid surgery.

METHODS

Literature Search

Two investigators independently conducted a search by using PubMed, Embase, and the Cochrane Library electronic databases for studies that were published up to 28 February, 2021. The search algorithm was [(Near-infrared) AND (parathyroid)] for PubMed. The following search terms were used in all fields as a search strategy for Embase: 1) parathyroid glands, parathyroid gland, parathyroid, parathyroids; 2) (spectroscopy, near-infrared), near-infrared spectroscopy, near infrared spectroscopy; near infrared, near-infrared. For Cochrane Library electronic databases, the search strategy was the following terms by searching Medical Subject Headings and free word in all field: 1) parathyroid glands, parathyroid gland, parathyroid, parathyroids; 2) (spectroscopy, near-infrared), near infrared spectroscopy, near infrared spectroscopies, near infra-red spectroscopy, near infra-red spectroscopies, near infrared, near infra-red. No restriction was imposed. In addition, we reviewed the reference lists of the retrieved papers and recent reviews.

Study Selection

The first screening was performed based on the title and abstract, and the full-text was then reviewed. A study was included when it met all the following criteria: 1) NIRAF was used to identify PG; 2) the data to calculate the sensitivity and/or specificity were reported; and 3) aforementioned data showed the numbers of PG. Studies were excluded based on the following criteria: 1) Conference Abstract, Review, Case report, Commentary, Discussion and Letter; 2) those in which the fluorescence originated from tracer; 3) those in which the trial was not conducted in human; 4) those which were published in non-English; 5) those from which data could not be collected adequately; and 6) those that the full text of the studies could not be accessed online or by request to the authors.

Data Extraction and Quality Assessment

Data were extracted by two reviewers (Wang B and Zhu CR) using a predefined data extraction form, and any disagreement between reviewers was resolved by consensus. Data were collected as follows: the first author, publication time, type of study, country of origin, study sites and institutes, measurement instrument and method, research period, sample size, the age of patients, disease (the reason for surgery) and surgical method, diagnostic standard and reference standard of PG, data to calculate the sensitivity and/or specificity. The quality of study was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (24).

Statistical Analysis

Combined sensitivity, combined specificity and summary receiver operating characteristic (SROC) curve were used to investigate the accuracy with Stata version 14.0 (Stata Corp LP, College Station, Texas, USA). The quality assessment of study was achieved through Review Manager 5.4. Meta-regression analysis was performed with removing the covariate with the largest P-value one by one by Meta-Disc 1.4. Heterogeneity was quantified statistically with the I² test. P < 0.1 and I² > 50% for heterogeneity were considered significant differences. We explored the reasons for heterogeneity by performing subgroup analyses. The measurement instrument, disease type and reference standard were examined as the potential influence factors on the accuracy of NIRAF. Potential publication bias was assessed by the Deeks’ funnel plots. P < 0.05 was considered statistically significant.

RESULTS

Literature Search

The study selection process is shown in Figure 1. A total of 214 potentially relevant records were identified through searching these databases and 2 other records were added by reviewing the reference lists of the retrieved papers. And one hundred and twenty-two records were retained after duplicates...
were removed. After screening the titles and abstracts, 84 studies were excluded for various reasons. The remaining 38 studies were assessed via full-text screening, and 14 studies were further excluded. Finally, 24 independent studies were included in the meta-analysis (14–16, 19–21, 25–42).

Study Characteristics
Table 1 summarizes the basic information of the 24 included eligible studies (14–16, 19–21, 25–42). These studies were published between 2013 and 2020 and all of them were prospective studies except one (16). Of the 24 studies, 3 were conducted in Asia, 8 in Europe, 11 in the United States, 1 in Argentina, and 1 in multicenter of American, France and Argentina. According to these studies, 11 types of instrument based on NIRAF were used to identify PG and a total of 2,062 patients and 6,680 specimens were included for analysis. The quality assessment of these studies was shown in Figure 2.

The Accuracy of NIRAF in Identifying PG
As shown in Figure 3, the overall combined sensitivity and specificity were both 0.96, and the area under curve (AUC) was 0.99. Significant heterogeneities were detected (Sen: $I^2 = 87.97\%$, Spe: $I^2 = 65.38\%$), but the publication bias did not appear significant as measured by the Deeks’ funnel plot asymmetry tests ($p=0.86$).

To address the heterogeneity, subgroup analysis was performed according to the measurement instrument, disease and reference standard. When the fluorescence spectroscopy system (spectrometer; S2000-FL; Ocean Optics, Dundelin, FL) was used, the combined sensitivity and specificity increased (Sen: 0.97, Spe: 0.98; Figure 4A) and the AUC was also 0.99 (Figure 4B), but the heterogeneities were still significant (Sen: $I^2 = 97.13\%$, Spe: $I^2 = 94.99\%$; Figure 4A). When the near infrared system (Tricam SL II, Karl Storz GmbH &Co KG, Tuttlingen, Germany) was used, although the heterogeneities decreased, the combined sensitivity was also decreased, and the combined specificity and AUC were not able to be combined because of lack of data (Figures 4C, D). When NIRAF was used during thyroid surgery and parathyroid surgery for primary hyperparathyroidism, the combined specificity decreased, but the combined sensitivity and AUC were same as the overall results and the heterogeneities did not also obviously change (Sen: 0.96, $I^2 = 86.97\%$, Spe: 0.95, $I^2 = 63.86\%$, AUC=0.99; Figures 5A, B). However, when NIRAF was used to identify
TABLE 1 | The characteristics of the included studies.

| Study ID | First author | Publication time | Type of study | Country/Region | Institute | Instrument | Measurement method | Research period | Patients (n) | Age (Mean ± Standard, Range) | Diagnostic standard | Disease | Surgical method | Reference standard |
|----------|--------------|------------------|---------------|----------------|-----------|------------|-------------------|----------------|-------------|-------------------------------|-------------------|---------|-------------------|-------------------|
| 1        | McWade       | 2013             | Prospective   | American       | Vanderbilt University | Fluorescence spectroscopy system (spectrometer; S2000-FL; Ocean Optics, Dundell, FL) | contact | NA           | 45 | NA                        | P/T:1.2          | T, pHPT, shPT | Tx, PTx           | Experience, Pathology reports |
| 2        | McWade       | 2014             | Prospective   | American       | Vanderbilt University | Fluorescence spectroscopy system (spectrometer; S2000-FL; Ocean Optics, Dundell, FL) | contact | NA           | 110 | NA                       | P/T:1.2          | T, pHPT, shPT | Tx, PTx          | Experience, Pathology reports |
| 3        | De Leeuw     | 2016             | Prospective   | France         | Université Paris-Saclay | Fluorescence spectroscopy system (spectrometer; S2000-FL; Ocean Optics, Dundell, FL) | Modified NIR imaging system (Karl Storz, PDD Camera B Segundo, CA) | 15cm | NA           | 3 | NA                        | Y                | T, pHPT, shPT | Tx, PTx          | Experience, Pathology reports |
| 4        | Falco        | 2016             | Prospective   | Argentina      | University of Buenos Aires/Cleveland Clinic Florida | Fluorescence imaging device (Fluobeam (Fluoptics, Grenoble, France)) | Modifed NIR imaging system (Karl Storz, PDD Camera B Segundo, CA) | 20cm | 2014-12-2015.3 | 63 | NA                       | Y                | T, pHPT, shPT | Tx, PTx          | Experience, Pathology reports |
| 5        | Kim          | 2016             | Prospective   | South Korea    | Kosin University | Fluorescence imaging device (Fluobeam (Fluoptics, Grenoble, France)) | 20cm | 2015.6-2015.8 | 28 | NA                       | P/B:1             | T, pHPT, shPT | TTx, PTx         | Experience, Pathology reports |
| 6        | McWade       | 2016             | Prospective   | American       | Vanderbilt University | Fluorescence spectroscopy system (spectrometer; S2000-FL; Ocean Optics, Dundell, FL) | contact | NA           | 137 | 53, 20-87                 | P/T:1.2          | T, HPT, PTx | Tx, PTx          | Experience, Pathology reports |
| 7        | Ladurner     | 2017             | Prospective   | Germany        | Ludwig Maximilians University Munich | Near-Infrared system (Tricam SL II, Karl Storz GmbH & Co KG, Tuttingen, Germany) | 5cm | NA           | 30 | NA                        | Y                | T, HPT, PTx | Tx, PTx          | Experience, Pathology reports |
| 8        | Alesina      | 2018             | Prospective   | Germany        | Universität Duisburg-Essen | Modular IMAGE1 S™ Camera (Karl Storz Endoskopie, Tuttingen, Germany) | NA | 2017.7-2017.8 | 5 | 56.2 ± 12.4, 45-77       | Y                | T, pHPT, shPT | TT, PTx          | Experience, Pathology reports |
| 9        | Kahramangil  | 2018             | Prospective   | American, France, Argentina | Cleveland Clinic Foundation, OH Hospital Europe, Marseille, France/Buenos Aires, Kosin University | Fluorescence imaging device (Fluobeam (Fluoptics, Grenoble, France)) | 20cm | NA           | 210 | 53.1 ± 14                | P/B:1             | T, pHPT, shPT | Tx, PTx          | Experience, Pathology reports |
| 10       | Kim          | 2018             | Prospective   | South Korea    | Ludwig Maximilians University Munich | Fluorescence imaging device (Fluobeam (Fluoptics, Grenoble, France)) | 20cm | 2015.7-2017.1 | 38 | 19-73                    | Y                | T                   | TTx, LTx         | Experience |
| 11       | Ladurner     | 2018             | Prospective   | Germany        | Ludwig Maximilians University Munich | Near-Infrared system (Tricam SL II, Karl Storz GmbH & Co KG, Tuttingen, Germany) | 5cm | NA           | 20 | NA                        | Y                | T                   | Tx            | Experience, Pathology reports |
| 12       | Thomas       | 2018             | Prospective   | American       | Vanderbilt University | Fluorescence spectroscopy system (spectrometer; S2000-FL; Ocean Optics, Dundell, FL) | contact | NA           | 162 | NA                        | P/T:1.2          | T, HPT, TT, PTx | Tx, PTx          | Experience, Pathology reports |
| 13       | DiMarco      | 2019             | Prospective   | United Kingdom | Hammersmith Hospital | Fluorobeam (Fluoptics, Grenoble, France) | 5cm | 2014.10-2019.4 | 117 | 49.9, 19-81              | Y                | T                   | pHPT, PTx       | Experience, Pathology reports |
| 14       | Kose         | 2019             | Prospective   | American       | Cleveland Clinic, Cleveland, Ohio Ludwig Maximilians University Munich | Near-Infrared system (Tricam SL II, Karl Storz GmbH & Co KG, Tuttingen, Germany) | 5cm | 2017.10-2018.5 | 50 | 47.2                     | Y                | T                   | HPT, PTx        | Experience, Pathology reports |
| Study ID | First author | Publication time | Type of study | Country/Region | Institute | Instrument | Measurement method | Research period | Patients (n) | Age (Mean ± Standard, Range) | Diagnostic standard | Disease | Surgical method | Reference standard |
|----------|--------------|------------------|---------------|---------------|-----------|------------|-------------------|----------------|-------------|---------------------------------|---------------------|---------|----------------|------------------|
| 17       | McWade       | 2019             | Prospective   | American      | Vanderbilt University | OTIS/Basler AG, Ahrensburg, Germany | 35cm | NA | 30 | 56.1 ± 11.7, 29-74 | P/B:1.5 | T, pHPT, shHPT | Tx, PTx | Experience, Pathology reports |
| 18       | Squires      | 2019             | Prospective   | American      | The Ohio State University - Wexner Medical Center | PDE-Neo II (Hamamatsu, Mitaka USA, Inc) | 5cm | 2017.6-2018.2 | 59 | P/T:1.1 | pHPT | PTx | Pathology reports |
| 19       | Thomas       | 2019             | Prospective   | American      | Vanderbilt University | PTeye | contact | NA | 20 | 46.8 ± 14.2, 21-70 | P/T:1.2 | T, pHPT, shHPT | TT, PTx | Experience, Pathology reports |
| 20       | Thomas       | 2019             | Prospective   | American      | Vanderbilt University | PDE-Neo II (Hamamatsu, Mitaka USA, Inc) | 5cm | 2018.12-2019.1 | 20 | NA | P/B:1.1 | T, pHPT | TT, PTx | Experience, Pathology reports |
| 21       | Wolf         | 2019             | Retrospective | Germany       | Schwarzwald-Baar Klinikum Villingen-Schwenningen | Near-infrared system (Tricam SL II, Karl Storz GmbH & Co KG, Tuttlingen, Germany) | 2-3cm | 2012.2-2019.9 | 39 | NA | Y | HPT | PTx | Pathology reports |
| 22       | Akbulut      | 2020             | Prospective   | American      | Cleveland Clinic, Cleveland, Ohio | Fluobeam (Fluoptics, Grenoble, France) | 20cm | 2018.7-2020 | 200 | 54.5 | P/B:1 | T, HPT | Tx, PTx | Experience, Pathology reports |
| 23       | Kose         | 2020             | Prospective   | American      | Cleveland Clinic, OH | Fluobeam (Fluoptics, Grenoble, France) | 15cm | 2016.7-2018.10 | 310 | 55.6 ± 15.2 | P/B:1 | T, pHPT | Tx, pPTx | Experience, Pathology reports |
| 24       | Takahashi    | 2020             | Prospective   | Japan         | Niigata University | PDE-Neo/Hamamatsu Photonics, Hamamatsu, Japan | 5cm | 2019.7-2019.12 | 36 | 61 ± 15.4 | P/T:1 | T | Tx | Pathology reports |

NA, Not Available; P/T, the ratio of fluorescence intensity for parathyroid/thyroid; P/B, the ratio of fluorescence intensity for parathyroid/background; Y, fluorescence was obtained; T, thyroid disease; HPT, hyperparathyroidism; pHPT, primary hyperparathyroidism; shHPT, secondary hyperparathyroidism; Tx, thyroidectomy (hemi- or total); TTx, total thyroidectomy; PTx, parathyroidectomy.
FIGURE 2 | Risk of bias and applicability concerns summary: review authors’ judgements about each domain for each included study.
normal PG during thyroid surgery, the combined sensitivity and specificity both increased (Sen: 0.98, Spe: 0.99; Figure 5C) and the AUC kept stable (AUC=0.99, Figure 5D), but the heterogeneities decreased (Sen: $I^2 = 59.71\%$, Spe: $I^2 = 67.65\%$; Figure 5C). When subgroup analysis was performed according to the reference standard, the combined sensitivity, combined specificity and AUC were respectively 0.97, 0.97 and 0.99 in the subgroup of experience (Figures 6A, B), and 0.96, 0.93 and 0.98 in the subgroup of pathology report (Figures 6C, D). The heterogeneities increased in the subgroup of experience (Sen: $I^2 = 92.88\%$, Spe: $I^2 = 68.83\%$, Figure 6A), while they reduced in the subgroup of pathology report (Sen: $I^2 = 57.27\%$, Spe: $I^2 = 55.15\%$, Figure 6C).

Although the heterogeneities got diminished in the subgroup of near infrared system (Tricam SL II, Karl Storz GmbH &Co KG, Tuttlingen, Germany), thyroid surgery and pathology report, they were still significant. We further performed meta-regression and found that the type of disease was related to heterogeneity ($P = 0.01$, Table 2).

**DISCUSSION**

The present meta-analysis demonstrated that NIRAF had a high accuracy in identifying PG during thyroid and parathyroid surgery, and the measurement instrument, status of PG and the reference standard of diagnosis of PG would influence the identification accuracy.

Some studies suggested that the accuracy of NIRAF in identify PG was closed to 100% (30, 41, 42). While, some other researchers got the result that the accuracy was less than 85% (15, 16). The difference in measurement instruments might be a reason for the difference in accuracy and the high heterogeneity across these studies. As described by Solorzano (43), all the approaches for NIRAF detection were based on probe or image, and different approaches had respective advantages and disadvantages, and thus these characteristics of different approaches might result in the difference in the identification accuracy. Due to the lack of data, the subgroup analysis of measurement instrument was only performed in two types of instrument. And we found that the heterogeneity decreased in the subgroup of near infrared system (Tricam SL II, Karl Storz GmbH &Co KG, Tuttlingen, Germany). Di Marco (44) and Solorzano (45) also reviewed the studies that NIRAF was used in thyroid and parathyroid surgery, but they did not perform the meta-analysis.

On account of the subjectivity of experience, the reference standard of diagnosis of PG was also regarded as an influence factor to be performed subgroup analysis. In the subgroup where pathology report was considered as reference standard, the heterogeneity diminished significantly. Although the surgeons in these studies were all senior professional endocrine surgeons, their experience and ability to identify PG might not be still fully consistent.

Surgical method depends on the type of disease, which means that PGs was normal in thyroid surgery and was hyperplastic in parathyroid surgery for primary or/and secondary...
hyperparathyroidism. When we performed subgroup analysis according to the type of disease, the heterogeneity became moderate in the subgroup of thyroid disease. And the meta-regression analysis also confirmed that the type of disease was significantly related to the heterogeneity. McWade et al. (25) and Kose et al. (34) found that the fluorescence intensity of hyperplastic PG was larger than that of normal PG, while DiMarco (33) and Squires (38) suggested that there was no significant difference in fluorescence intensity between hyperplastic PG and normal PG, but Falco (26) and Aoyama (46) reported that the fluorescence of hyperplastic PG was weaker than that of normal PG. The inconsistent results of comparison of fluorescence intensity between hyperplastic PG and normal PG might affect PG identification and thus cause the heterogeneity. The reason for the difference in fluorescence intensity of hyperplastic PG might be

![Image](https://example.com/image.png)
that the fluorescence intensity of PG with primary hyperparathyroidism was stronger than that of PG with secondary hyperparathyroidism and the fluorescence intensity distributed unevenly in hyperplastic PG (47). Wolf and colleagues reported a lower accuracy in identifying PG during surgery for secondary hyperparathyroidism than that during surgery for primary hyperparathyroidism (16). However, we could not verify this result, because the subgroup analyses were not able to be performed in the subgroup of primary and secondary hyperparathyroidism on account of lack of data.

Several limitations existed in this meta-analysis. First, data of sensitivity and specificity could not be collected at the same time in some studies. Second, although we performed subgroup analysis, the heterogeneity did not disappear. Third, some subgroup analyses could not be performed because of lack of eligible data. Fourth, the diagnostic standards were not uniform among these studies, even though no threshold effect was observed in this meta-analysis. Lastly, the exclusion of non-English-language studies might lead to bias.
CONCLUSION

In conclusion, the NIRAF is an excellent indicator for identifying PG during thyroid and parathyroid surgery, and the accuracy is perfect, especially in thyroid surgery. The ability of NIRAF to preserve PG function during thyroid surgery is worth exploring.
DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS
Study conception and design: BW, C-RZ, HL, X-MY, and JW. Acquisition of data: BW and C-RZ. Analysis and interpretation of data: BW, C-RZ, and HL. Drafting of manuscript: BW and C-RZ. Critical revision: BW, C-RZ, HL, X-MY, and JW. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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