Establishing the clinical utility of autofluorescence spectroscopy for parathyroid detection

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Background. *The inability of surgeons to identify parathyroid glands accurately during cervical endocrine surgery hinders patients from achieving postoperative normocalcemia. An intrinsic, near-infrared fluorescence method was developed for real-time parathyroid identification with high accuracy. This study assesses the clinical utility of this approach.*

Methods. *Autofluorescence measurements were obtained from 137 patients (264 parathyroid glands) undergoing parathyroidectomy and/or thyroidectomy. Measurements were correlated to disease state, calcium levels, parathyroid hormone, vitamin D levels, age, sex, ethnicity, and body mass index. Statistical analysis identified which factors affect parathyroid detection.*

Results. *High parathyroid fluorescence was detected consistently and showed wide variability across patients. Near-infrared fluorescence was used to identify 256 of 264 (97%) of glands correctly. The technique showed high accuracy over a wide variety of disease states, although patients with secondary hyperparathyroidism demonstrated confounding results. Analysis revealed body mass index ($P < .01$), disease state ($P < .01$), vitamin D ($P < .05$), and calcium levels ($P < .05$) account greatly for variability in signal intensity. Age, sex, parathyroid hormone, and ethnicity had no effect.*

Conclusion. *This intrinsic fluorescence-based intraoperative technique can detect nearly all parathyroid glands accurately in real time. Its discrimination capacity is largely unlimited by patient variables, but several factors affect signal intensity. These results demonstrate potential clinical utility of optical guidance for parathyroid detection. (Surgery 2016;159:193-203.)*

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INSUFFICIENT OR INACCURATE IDENTIFICATION OF THE PARATHYROID GLANDS during thyroidectomy and parathyroidectomy procedures can lead to operative complications. The incidence of inadvertent parathyroidectomy during thyroidectomy ranges from 8 to 19%[1] and may result in postoperative hypocalcemia. Operative cure for patients with hyperparathyroidism is dependent on adequate resection of hypersecreting parathyroid glands. If not accomplished, patients may experience persistent hyperparathyroidism and require reoperation. The development of preoperative parathyroid imaging modalities has improved operative success rates[2]; however, surgeons must still rely on visual assessment during surgery to identify parathyroid glands. The accuracy of this approach is highly dependent on the experience level of the surgeon.[3]

Detecting the parathyroid presents the greatest difficulty in cases such as total thyroidectomy, completion thyroidectomy, central neck lymph node dissection, and reoperative thyroid and parathyroid procedures. The larger extent of dissection during total thyroidectomy and central neck lymphadenectomy poses greater risk of inducing iatrogenic surgical trauma and compromised blood supply to the parathyroid glands.[4] Difficulty in

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reoperative and completion thyroidectomy procedures is attributable to the formation of scar tissue and fibrosis, which distorts normal dissection planes and anatomic relationships.[5] During parathyroidectomy, ectopic glands and multiple gland disease also present obstacles to adequate resection and surgical success.[3] Intraoperative rapid parathyroid hormone assay is one technique for confirming complete removal of hyperfunctioning glands and in some cases to confirm the correct identification of parathyroid tissue. Intraoperative parathyroid aspiration is another technique for confirmation that requires finding the gland, aspirating it with a needle, and analyzing the aspirate for PTH.[6] There remains a clinical need for an intraoperative technique to detect the parathyroid gland instantly and with high accuracy.

To fill this clinical need, we have previously demonstrated the capability of a novel parathyroid detection technique using near-infrared (NIR) fluorescence spectroscopy.[7-9] The parathyroid glands have been shown to emit a NIR autofluorescence signal that is stronger than that of the thyroid and all surrounding tissues in the operative bed. Unlike current preoperative parathyroid-detection modalities, this method provides real-time, intraoperative feedback with high accuracy. Intrinsic fluorescence is the basis of this technique, which obviates the need for potentially nonspecific or toxic external contrast agents. The fluorophore in the parathyroid gland currently is unknown. A more thorough understanding of the sources contributing to variability in parathyroid fluorescence intensity is necessary and may provide insight into the fluorescence etiology.

This new operative technique must be proven to be capable of handling the full spectrum of interpatient variability before its clinical adoption. The goal of our study, then, is to establish the clinical utility for this novel intraoperative parathyroid detection technique by assessing the effects of pathologic, clinical, and demographic patient variables on the parathyroid fluorescence signal. We present NIR fluorescence spectra acquired from patients undergoing cervical endocrine surgery. Patient factors such as body mass index (BMI), metabolite levels, disease type, or hormone levels, age, and sex underwent statistical analysis for their effects on the parathyroid detection rate. The results suggest NIR fluorescence spectroscopy is ready for clinical implementation as a parathyroid detection tool by showing its effectiveness over a variety of clinical presentations.

METHODS

Patient selection. Informed, written consent from all patients enrolled in the study which was approved by the Institutional Review Board (IRB) of Vanderbilt University (#070795). All patients 18–99 years of age who presented at the Vanderbilt Endocrine Surgery Center for thyroidectomy and/or parathyroidectomy were eligible for enrollment into the study. Patient eligibility was evaluated by the attending surgeon during preoperative assessment at the Vanderbilt University Endocrine Surgery Center. One hundred thirty-seven patients were enrolled for intraoperative fluorescence detection of the parathyroid glands.

Fluorescence measurement. The surgery was conducted as called for by the disease presentation. During dissection, at least 1 parathyroid gland was identified. The tissue was exposed such that the 2 mm tip of the optical probe could directly contact the surface of the tissue. NIR autofluorescence spectra were collected from parathyroid, thyroid, muscle, and fat with the use of a custom, portable NIR fluorescence spectroscopy system.[7,9] A total of 264 parathyroid glands from 137 patients were measured with 1–4 glands measured per patient. The system consists of a 785-nm diode laser (I0785SL0050PA; IPS, Monmouth Junction, NJ), sterile fiber optic probe (EMVision, Loxahatchee, FL), and spectrometer (S2000-FL; Ocean Optics, Dunedin, FL) all controlled by a laptop computer. The fiber optic probe irradiated tissue with 80 mW of light and a 400-μm spot size for an integration time of 300 ms. Six spectra were collected per tissue site with the overhead lights turned off, with approximately 4 seconds taken for each spot measured Fluorescence measurements were validated with tissue histology as the gold standard when available. In cases in which the parathyroid was not removed, the confidence level of the surgeon in their visual identification was noted (high, medium, or low). Low confidence measurements were excluded from the study. To account for day-to-day system variations, each fluorescence spectra from a given patient was divided by the peak fluorescence intensity of the thyroid of that same patient to yield what is referred to throughout the study as normalized fluorescence. Further calibration and postprocessing was performed as described previously.[7] Parathyroid glands were deemed "undetectable" if their normalized peak fluorescence intensity was less than 1, because this indicated the parathyroid