OBJECTIVE

The variable location and indistinct external features of parathyroid glands can make their intraoperative identification challenging.1,2 Currently, there exists no routine use of noninvasive localization methods during surgery. Dynamic Optical Contrast Imaging (DOCI) leverages a novel realization of temporally dependent measurements of tissue autofluorescence that allow the acquisition of specific tissue properties over a large field of view. The objective of this study is to demonstrate the utility of DOCI in reliably and accurately identifying parathyroid glands and differentiating them from surrounding neck tissues.

METHODS

Study Design: A prospective series of patients diagnosed with primary hyperparathyroidism at the David Geffen School of Medicine at UCLA was examined. Parathyroid adenomas and their surrounding tissues in the surgical bed were collected; fluorescence decay images were acquired using a wide-field DOCI system. 127 Samples (81 patients) were subsequently processed for standard histological assessment (T1). Mean relative fluorescence decay signatures were calculated for parathyroid, fat, thyroid, and thymus tissues.

RESULTS

Our DOCI system extracts relative fluorescence decay information (Fig 1) in a surgically relevant field of view with a clinically accessible acquisition time < 2 minutes. We demonstrate the feasibility of utilizing DOCI to rapidly distinguish parathyroid tissue from surrounding tissue (Fig 2). Analysis of DOCI images revealed microscopic characterization sufficient for tissue type identification consistent with histology.

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1 Fluorescence decay signatures and ROI localization

(a) Visible

(b) DOCI

(c) Histology

Figure 1. (a) Gross images of parathyroid glands. (b) DOCI images (c) Co-registered histologic sections.

ROIs have been drawn by a physician (blinded to DOCI images) which are then superimposed onto DOCI (white: parathyroid; black-fat).

The system, consisting of UV-LEDs and an intensified CCD camera, captured images of the fluorescence decay signatures. The obtained fluorescence images were normalized with each other by dividing the decay image with the calibration image. DOCI and visible images were automatically co-registered, as they were acquired from the same aperture. Using Matlab, ROIs were drawn on the visible images. The pixels contained in the ROIs were then grouped by tissue type and evaluated for statistical significance.

2 Average relative fluorescence lifetimes of different tissue types

The computed p-values are plotted in Figure 2(b) in negative log10 scale where a p<0.05 was labeled as significant. Figure 2(b) is displayed in the style of a Manhattan plot where smaller p-values (increased significance) are mapped to larger bars in the bar plot. Further, the 0.05 threshold is denoted with the gray shaded area in Figure 2(b). All bars above the threshold are labeled significant.

The p-values for the parathyroid-fat, parathyroid-thymus, and parathyroid-thyroid pairs are denoted with the red, green, and blue bars respectively. Significance was observed between parathyroid and non-parathyroid for all ten band-pass filters. In general, the middle wavelength filters (460nm–594nm) provided better qualitative contrast between thymus and parathyroid, while all wavelengths provided statistically significant contrast between parathyroid vs. fat and parathyroid vs. thyroid.

Table 1. Tissue Types. This table shows the categorization of various tissue types collected and imaged by the DOCI system. A total of 127 specimens were collected.

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>43</td>
</tr>
<tr>
<td>Parathyroid</td>
<td>66</td>
</tr>
<tr>
<td>Thymus</td>
<td>9</td>
</tr>
<tr>
<td>Thyroid</td>
<td>9</td>
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</tbody>
</table>

DISCUSSION

This study provides ex vivo data that has implications for making DOCI a reliable in vivo technique to produce a “relative decay map” of tissues, depicting analyzable color contrasts that correspond to parathyroid gland location. DOCI utilizes safe light and precludes the use of invasive dyes3 or radioactive material injection, avoiding the concerns for allergic reactions or radiation exposure.4 The process of imaging and map formulation takes less than two minutes and is significantly faster than intraoperative frozen section analysis, a process that not only adds 20-30 minutes to anesthesia time but can cost $500 per sample.5,6 Furthermore, DOCI has the potential to help identify and therefore perhaps avoid the inadvertent removal of normal parathyroid gland during challenging thyroidectomies. Accidental removal of healthy parathyroid glands during neck dissections can cause transient hypocalcemia in 20-30% of cases,7 while permanent hypoparathyroidism may lead to life-long calcium supplementation.8,9

The basis of tissue contrast in the DOCI parathyroid images is likely correlated to the increased calcium content of the parathyroid hormone8 and the presence of hormone specific proteins and amino acids. The autofluorescence and lifetime fluorescence of these substances have not yet been investigated in the context of parathyroid tissues, but they have been studied extensively as isolated samples and support the utilization of calcium and parathyroid hormone specific proteins as the basis for imaging contrast.9,10

CONCLUSION

This study demonstrates a new imaging modality capable of efficiently distinguishing parathyroid tissue from adjacent tissues. Such an intraoperative tool would be transformative in gland localization, enabling the surgeon to effectively identify lesions, preserve healthy tissue, and improve patient outcomes.

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References