Diffuse Optical Imaging of ICG Dynamics in the Diseased Breast with High Temporal Resolution

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Abstract: Following intravenous ICG bolus injection, we obtained diffuse optical 3D images of the absorption contrast dynamics in the breast on 20 patients. We identified lesions based on local perfusion characteristics using a General Linear Model.

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1. Introduction

Diffuse optical tomography (DOT) has been explored as a diagnostic modality for neoplastic disease of the breast for about two decades. The initial goal of accurate reconstruction of static optical tissue parameters proved to put strong demands on instrumentation performance, calibration requirements, and/or computational complexity, and yielded unsatisfactory diagnostic power. More recently, researchers have begun to explore a wider space of optical measurables that are connected to the physiological and pathological states of tissue. Examples are the expansion of the detected spectrum from few to many discrete wavelengths (or even continuous spectra), the use of external absorption and/or fluorescent contrast agents, and the observation of tissue dynamics in image time series. The last has been combined with active or passive tissue provocation maneuvers (breathing maneuvers, pressure change, etc.).

One of the hallmarks of neoplastic tissue is the presence of neoangiogenesis, i.e., the formation of new blood vessels that (a) lead to greater local perfusion and (b) are structurally disturbed. In principle, both characteristics should be observable through contrast agent based imaging; local perfusion affects the amplitude of primarily the early components of a dye bolus, and the leakiness of tumor vessels may allow for increased passage of contrast agents into the interstitial space (extravasation).

Contrast-enhanced optical mammography studies using ICG have been reported before. Whereas fluorescence measurements demonstrated tumor-specific enhancement in the late uptake, these were far too slow to directly observe any perfusion-related dynamics [1]. Previously reported absorption measurements were able to study some aspects of the breast's ICG pharmacokinetics [2]; however, to our knowledge none of these have been performed at scan rates that adequately sample the early bolus dynamics in the tissue.

In this report we demonstrate the benefit of high-frame rate absorption tomography of ICG bolus kinetics for localizing breast lesions.

2. Methods

We used a DYNOT 232 optical tomography system (NIRx Medical Technologies LLC, NY, USA), which was customized for mammography studies. 31 fiber optic sensors, each containing an optical source and detector, were placed in contact with the breast by means of a rigid plastic cup. We accommodated different breast sizes by varying the protrusion of the fibers into the cup. A detailed description of the system is given in [3]. The fiber holder was mounted to a gantry positioned under a modified patient bed. The gantry slides sideways to be used on either breast and can be height-adjusted to bring the cup up against the patient's chest wall through an opening in the bed. The subjects were resting in a prone position throughout the experiment.

The study was approved by the hospital's ethics committee. We recruited 20 patients of the radiology clinic who had high probability for breast occupying lesions and who were scheduled for needle aspiration biopsy. Further inclusion criteria were: Age > 18 y, cup size ~34B, no operation or biopsy within the previous six months. Additionally, all subjects received Gd-DTPA contrast dynamic magnetic resonance (MR) imaging scans.

Before the measurement, an indwelling canula was placed in an superficial vein of the forearm, the patients were then asked to lie prone on the bed, and the optical fibers were placed on the diseased breast. Following system calibration procedures (measurement of dark current and adjustment of detector sensitivity) we record a resting – or baseline – phase (5 min.), after which we injected a single bolus of 25 mg ICG (Pulsion AG, Munich, Germany) in 15 ml saline solution. Care was taken to inject the bolus within 5-10 s. The scan then continued for about 20 min. after injection.
Data are analyzed using the NIRx NAVI software. Analysis starts with preprocessing; first, we apply a low-pass filter \( f_{\text{cutoff}} \approx 0.15 \text{ Hz} \) to suppress the heart beat and higher-frequency noise. We then exclude channels that exhibit excessive noise (C.V. > 25\%) during the rest phase and then normalize the data channels with respect to the temporal mean value during rest. From the preprocessed data we reconstruct 3D time series of relative ICG concentration changes. Time series images are reconstructed with the normalized-difference method using a pre-computed weight function that is generated using a finite element method (FEM) solver of the diffusion equation [4].

Because by default the NAVI software computes images of hemoglobin oxygenation changes based on two wavelengths (760 nm, 830 nm), we modified the conversion matrix to reflect absorption changes due to ICG concentration in the lower wavelength.

We based our analysis on a two-compartment model that only distinguishes 'lesion' from 'healthy' tissue. We used the measured data from two patients with confirmed focal malignant lesions to generate prototypical model functions for both tissue types, which we then used to localize lesion areas in all patients using a General Linear Model (GLM). For lesion detection we created t-value maps for the tumor model curve, with higher t-values signifying a better model fit, i.e. presence of 'tumor-like' perfusion.

3. Results

Fig. 1 shows the typical result of the reconstructed concentration changes for different image voxels as well as the averaged response over all voxels.

![Figure 1](image1.png)

**Figure 1.** Reconstructed absorption changes for a representative subject (77 y, 19mm metaplastic CA). Only 200 out of 2243 voxel time course displayed. The fat black curve represents the average over all voxels.

Some voxels show an initial bolus peak (starting at time 100 s, duration ~10-15 s) that is missing in the majority of curves as well as in the average response. We also observe significant drift in the late components in the time series (> 700 s). In our subsequent image analysis we focused on the early dynamics because (1) a pronounced bolus peak is characteristic for highly perfused tissue such as a tumor, (2) the peak seems to occur only in a fraction of the imaged volume and not in the average curve, thus pointing toward a localized phenomenon, such as a lesion. (3) Lastly, the late components, which in theory are indicative of possible extravasation, are much more prone to background drift, making this part much more difficult to analyze.

![Figure 2](image2.png)

**Figure 2.** (a,b) ICG absorption change for tumor area (blue) and normal background (green) as measured in two Ca patients. (c) GLM input functions of tumor and normal tissue, as derived from (a,b). Amplitude \( A \) and latency \( \Delta t \) are individually adjusted to the average response of each patient before starting GLM analysis.

Figs. 2 (a,b) present the reconstructed absorption dynamics from two patients with confirmed malignant regions. In both cases, we used the reconstructed image time series to define a region of interest at the tumor site – as confirmed by radiological findings and biopsy – from which we derived a spatially averaged ‘tumor’ response (blue).
All remaining voxel responses were averaged to represent ‘normal’ tissue (green). As can be seen, both cases show a remarkably similar response. From both cases we created average ‘tumor’ and ‘normal tissue’ curves (c) to act as model functions in the subsequent GLM analysis. Before averaging, curves were time-shifted and normalized to their respective peak heights.

Fig. 3 shows some representative comparisons of dynamic ICG tomography and the corresponding Gd-DTPA-enhanced dynamic MR images. The lesion location in both modalities show excellent agreement.

![Representative results from three patients. Top to bottom: mediolateral, coronal, craniocaudal sections. All panels: left: MR, right: DOT(a) 37 y, 22-mm IDC. (b) 68 y, 16-mm IDC. (c) 27 y, 22-mm fibroadenoma.](image)

Table 1 summarizes all cases imaged and the detection rates for benign and malignant lesions. The malignant detection rate of 10/14 is very encouraging. We also detected half the benign lesions (3/6); however, using our current analysis approach we cannot differentiate those from malignant tumors.

<table>
<thead>
<tr>
<th>Malignant</th>
<th>Detection Rate</th>
<th>Benign</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ductal carcinoma (IDC)</td>
<td>7 / 9</td>
<td>Fibro-cystic mastopathy</td>
<td>2 / 3</td>
</tr>
<tr>
<td>Invasive lobular Ca (ILC)</td>
<td>0 / 2</td>
<td>Fibroadenoma</td>
<td>1 / 2</td>
</tr>
<tr>
<td>Metaplastic carcinoma</td>
<td>1 / 1</td>
<td>Pseudoangiomatous stromalhyperplasia (PASH)</td>
<td>0 / 1</td>
</tr>
<tr>
<td>Ductal carcinoma in situ (DCIS)</td>
<td>1 / 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma metastasis</td>
<td>1 / 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sum</strong></td>
<td><strong>10 / 14</strong></td>
<td></td>
<td><strong>3 / 6</strong></td>
</tr>
</tbody>
</table>

4. Conclusions

High-frame rate optical imaging is capable of localizing early ICG enhancement following bolus injection and allows differentiation between focal mammographic lesions and healthy breast tissue. Our current approach does not provide clear differentiation between benign and malignant lesions. To improve specificity, the evaluation of late ICG enhancement as a marker for extravasation would be desirable.

5. References


