Multicolor frequency-domain diffuse optical tomography for detection of breast cancer

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ABSTRACT

Diffuse Optical Tomography (DOT) is based on acquiring information from multiply scattered light which penetrates into the tissue up to depths of several centimeters. This technique allows for imaging of absorbing and scattering inclusions inside tissue and distinguishing between them after computer processing of an image. An experimental setup for multicolor frequency-domain diffuse optical tomography (FD DOT) to visualize neoplasia of breast tissue and to estimate its size has been created. A breast is scanned in the transilluminative configuration by a single source and detector pair. Illumination at three wavelengths (684 nm, 794 nm, and 850 nm) which correspond to different parts of the absorption spectrum provides information about concentration of the main absorbers (oxygenated hemoglobin, deoxygenated hemoglobin, and fat/water). Source amplitude modulation at 140 MHz increases spatial resolution and provides separate reconstruction of scattering and absorption coefficients. *In vivo* study of breast carcinoma has been performed. Maps of 2D distributions of reconstructed absorption and scattering coefficients and concentration of hemoglobin have been obtained. An increase of absorption and scattering coefficient, total hemoglobin concentration and decrease of blood oxygen saturation is observed in the tumor area in comparison with the surrounding tissue. We can conclude that FD DOT technique confirms a possibility of detecting neoplastic changes.

Keywords: breast cancer; frequency-domain diffusion optical tomography; photon density waves.

1. INTRODUCTION

Early diagnostics of breast cancer provides good chances of a recovery. Currently, conventional diagnostic methods for breast cancer include ultrasonic examination and X-ray mammography. Although the method of mammography is highly efficient, it has several limitations: low sensitivity for women with dense breast tissue and for young women, as well as poor informativity for determination of tumor type (benign-malignant) [1–4]. Mammography is not recommended for follow-up and treatment monitoring due to ionizing radiation used in this method. Ultrasonic examination demonstrates relatively low sensitivity of early cancer detection and low specificity for aged women due to breast involution [5, 6]. It may provide additional information to mammography and can be useful for detecting the focal breast disease in women under 35 [6].

Optical methods are very attractive for medical diagnostics due to their noninvasiveness and sensitivity. Diffuse Optical Tomography (DOT) [7–11] is a technique based on acquiring information from multiply scattered light that penetrates into tissue at depths up to several centimeters. This technique allows imaging of absorbing and scattering inclusions inside tissue after computer processing of an image. DOT is applicable for a variety of studies, such as breast cancer detection, investigation of brain and muscle functional activity, location of intracranial traumatic haematomas [12–14], when there is a need to visualize deep tissue structures or processes. Some encouraging results were recently obtained by several research groups in clinic for detection of breast cancer [9, 14–19] and for monitoring therapy response [20]. Strong scattering blurs sharp edges of an inhomogeneity thus reducing spatial resolution down to 0.5 cm. Frequency-domain (FD) (or photon density waves) technique employs illumination of the tissue by amplitude-modulated light [7, 8]. This method significantly increases spatial resolution of the observed objects inside turbid media due to registration and processing of the amplitude and phase of signal envelope which both carry information about the tissue scattering and absorption inclusions.

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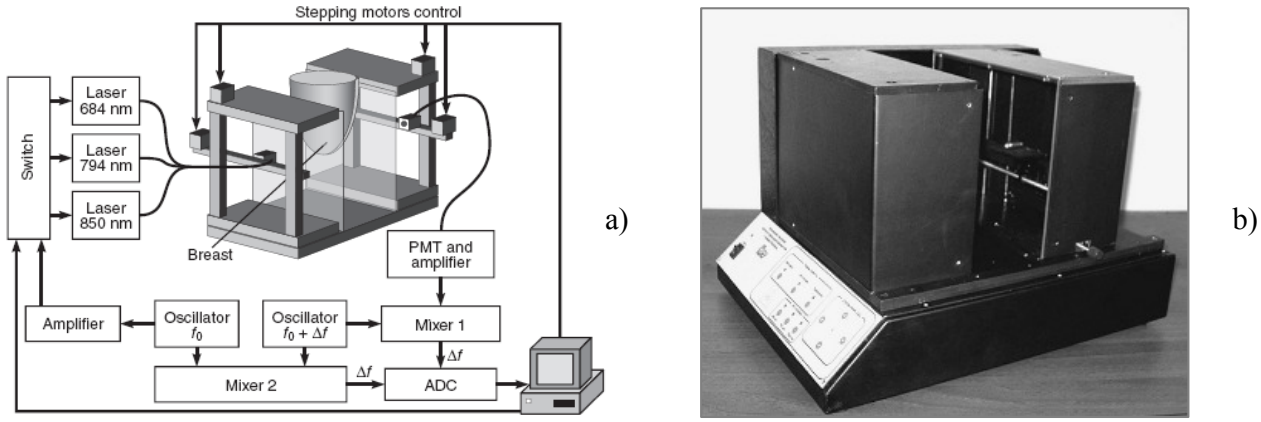
In the transparency window (λ = 600-1100 nm) absorption in biotissues is determined primarily by four components [8–11]: lipids, water, oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (HHb). Due to different dependence of the components absorption coefficient on wavelength it is possible to estimate tissue composition. Normal, benign and malignant tissues differ in concentrations of hemoglobin, lipids, degree of blood oxygenation and water content [14, 16], so the data about their distribution in tissue obtained by DOT at different wavelengths may be useful for diagnostics.

In this paper we present the results of initial clinical experiments utilizing the FD DOT setup created at the Institute of Applied Physics (Russia). The laser source wavelengths are 684 nm, 794 nm, and 850 nm. These wavelengths are chosen because in the vicinity of 700 nm deoxyhemoglobin makes the main contribution to absorption, the wavelength of 794 nm corresponds to equal absorptions of deoxyhemoglobin and oxyhemoglobin, and oxyhemoglobin is the dominating absorber at 850 nm. The ability of DOT method to investigate the internal structure of deep tissues is demonstrated. 2D maps of absorption and scattering coefficients at three wavelengths as well as maps of tissue components distribution show the differences in malignant and surrounding normal tissues.

2. MATERIALS AND METHODS

Eight patients 30-78 years old with diagnosis of breast carcinoma were involved in the preliminary clinical study. In every case, ultrasonic investigation of breast was performed before DOT examination. So we possessed the information about the location and the dimension of the investigated tumor. DOT was used before mastectomy and following histological verification of the removed tissue.

Experiments on DOT were performed on the experimental setup with parallel plane geometry created at the Institute of Applied Physics RAS (Nizhny Novgorod, Russia, Fig. 1). The investigated breast is gently pressed between two glass plates, the source plane and the receiving plane, and scanned in the transilluminative configuration by a single source and detector pair. Three laser fibers coupled in a single bundle illuminate the studied volume at 684 nm, 794 nm, and 850 nm. The frequency of amplitude modulation is f_0 = 140 MHz. Independent scanning of source and detector in corresponding planes is performed by computer controlled stepping motors; scanning area is 15x15 square centimeters. Data reading at three wavelengths is realized by automated sequential switching from one laser to another at each source-detector position. Calculation of signal amplitude and phase is done by means of a computer. The diffuse light is detected by the Hamamatsu photomultiplier tube with automatic gain control. Sensitivity of the receiving system is approximately 2×10^{8} mW. Determination of component composition was performed as described in [21].



a) b)

Figure 1. Functional scheme (a) and design (b) of the FD DOT experimental setup.

3. RESULTS

The first step of the investigation was obtaining of amplitude and phase of the photon-density wave ODT images of breast tissue at 3 wavelengths. In Fig. 2 we show images obtained from a 48-year-old patient with diagnosis of invasive

breast carcinoma T1N0M0, I stage. The images were acquired by simultaneous scanning of source and detector facing each other, with fixed source-detector separation (50 mm); DOT imaging area was 90×50 mm. It is clear from the DOT images the tumor zone can be clearly distinguished from the surrounding normal tissues (Fig. 3c). The tumor zone is characterized by a low level of signal amplitude observed at all the three wavelengths. This inhomogeneity can be seen in phase images as well. According to the results of ultrasonic examination (Fig 2a), the size of the focal lesion was 10×7×9 mm, which is in good agreement with data obtained by DOT. Histological investigation of breast tissue detected carcinoma characterized by scirrhous structure with modified blood vessels, increased tumor matrix content and minor lipid inclusions (Fig. 2b).

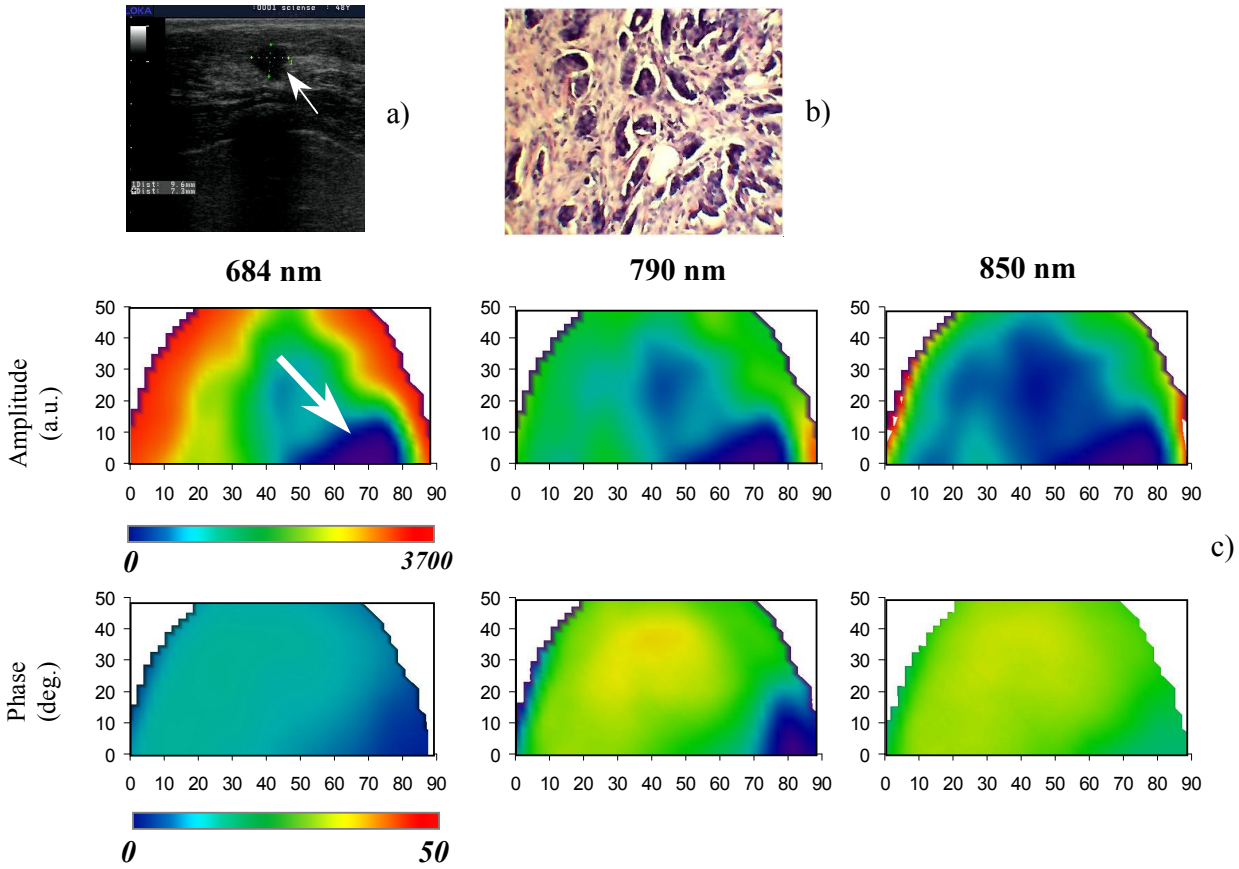


Figure 2. Invasive breast carcinoma T1N0M0, I stage. Ultrasonic image (a), histological specimen – scirrhous carcinoma, 200×10 (b), and maps of 2D distributions (90×50 mm) at 3 wavelengths (table) of raw (amplitude and phase of the photon-density wave) data. The arrow shows the tumor region.

The second step of the investigation was the reconstruction of distribution of absorbing and scattering inclusions in the region of interest as well as reconstruction of distribution breast tissue components. Such data gives an additional information about structural and functional changes in the tumor zone. Maps of the reconstructed distributions of absorbing inclusions demonstrate the presence of the zone with high absorption at 684, 794, and 850 nm in the tumor region (Fig. 3). Also observed was an increase of scattering coefficients in the tumor zone at all wavelengths. This can be explained by increased organelles number and extracellular matrix content in tumor region [22].

Reconstructed distributions of HHb, HbO_2 concentrations, and oxygen saturation (StO2) are shown in Fig. 4. Oxygen saturation was calculated by the formula $StO_2 = [HbO_2]/[HHb + HbO_2]$. Figure 4 demonstrates that the concentration of both oxy- and deoxyhemoglobin in the tumor zone is higher than in the surrounding tissue. In tumor zone, change of concentration of HbO_2 is greater than change of HHb content.

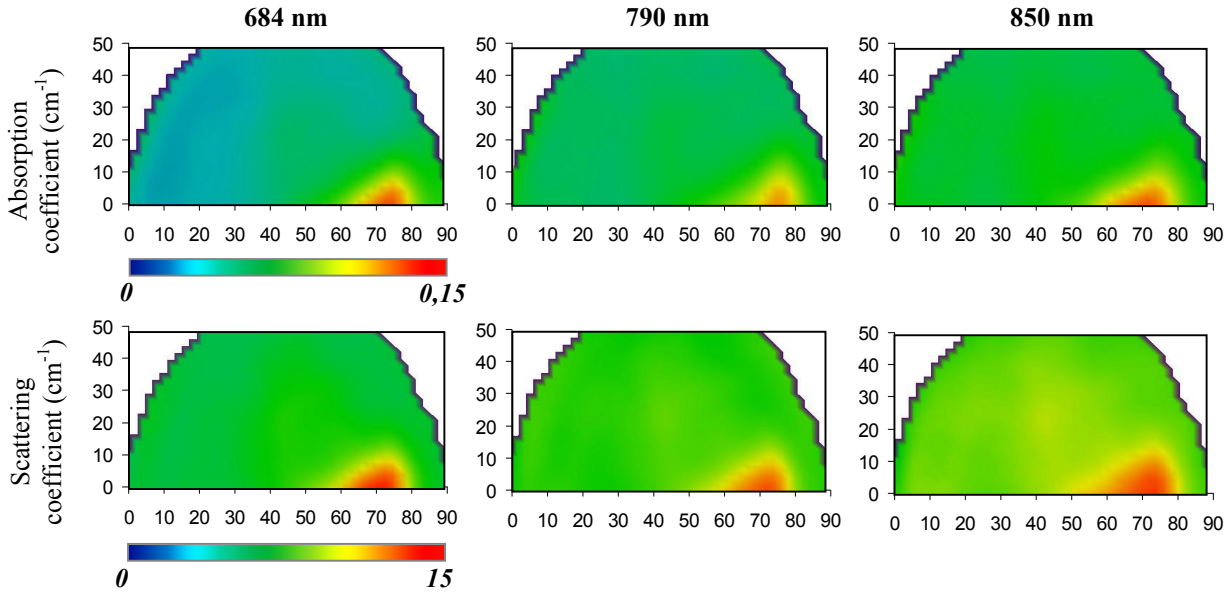


Figure 3. Maps of 2D distributions (90×50 mm) at 3 wavelengths of reconstructed (absorption and scattering coefficients) data.

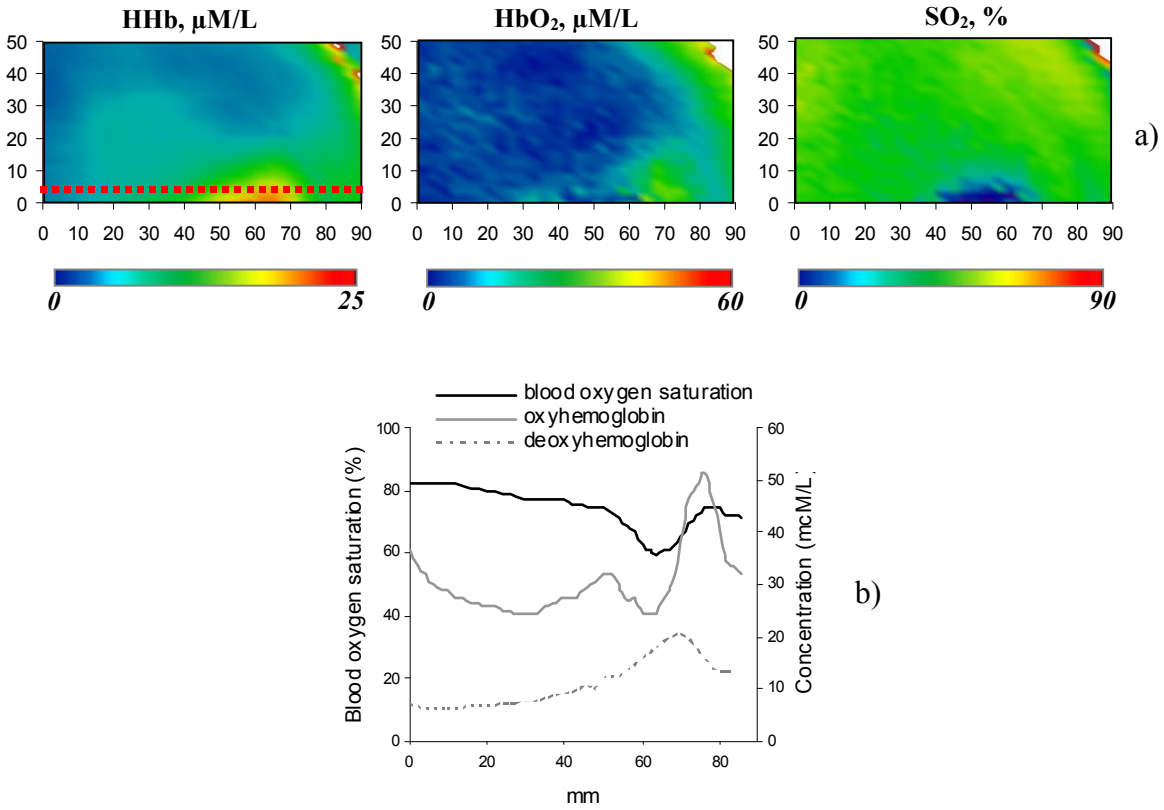


Figure 4. Reconstructed concentrations of deoxyhemoglobin (HHb), oxyhemoglobin (HbO_2), and oxygen saturation (StO_2) by the data shown in Fig. 2 (a) and profile at $y = 2$ mm (b).

It should be noted that in majority of cases regions with high HHb concentration are located in the central part of the tumor whereas regions with high HbO_2 concentration are detected at the periphery (Fig. 4b). Oxygen saturation in tumor is lower than in surrounding breast tissue. Distribution of oxygenated and deoxygenated forms of hemoglobin may reflect features of oxygen exchange in tumor tissues and tumor vascularisation. Large number of blood vessels deliver oxygen to tumor cells, which are characterized by increased metabolic activity. Newly formed microvessels in most solid tumors do not conform to the normal morphology of the host tissue vasculature, they exhibit a series of severe structural and functional abnormalities [23], and so they cannot satisfy the need of rapidly growing tumor tissue for oxygen. As a result, the regions with low oxygen content appear in the tumor focus [24, 25] that can be observed as zones with high HHb level and low blood oxygen saturation. Estimation of the capability of DOT to determine characteristics of intratumoral zones becomes possible after verification of tissue oxygen status by several additional methods.

4. CONCLUSION AND FUTURE DIRECTIONS

We can conclude that the DOT technique confirms a possibility of investigating the internal structure of deep tissues and of detecting neoplastic changes. The sensitivity of the created system allows one to locate tumors at the thickness of the studied breast 8 cm or less. The observed increase of scattering and absorption coefficients in the area of the carcinoma provides information about location, size, and structural features of a tumor. Illumination at multiple wavelengths provides determination of component distributions under appropriate image processing. Data on blood oxygen saturation obtained by DOT may show physiological differences not only between normal and tumor tissue for diagnostics but also between several tumor zones for tissue characterization that can be essential for prognosis and therapy selection. In our future experiments, we plan to perform several additional experiments aimed at verification of DOT results by conventional methods of determination of tissue oxygen status.

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