

Diffuse optical measurement of blood flow in breast tumors

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Blood flow contrast between tumor and normal tissues in patients with malignant and benign breast cancer was measured by diffuse optical correlation methods. The measurements were carried out with a hand-held optical probe that was manually scanned over the tumor-bearing breast. Increased blood flow was observed in tumor regions relative to healthy tissue, and control subjects did not exhibit significant blood flow heterogeneity. The measurements introduce a new optical contrast for diffuse optical mammography. © 2005 Optical Society of America
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Near-infrared (NIR) diffuse optical spectroscopy (DOS) and diffuse optical tomography (DOT) of the breast¹⁻⁵ offer novel contrast for tumor characterization and detection, with promise for longitudinal monitoring of tumor therapy.^{6,7} In clinical studies, for example, the diffuse optical methods have revealed tumor contrast to varying degrees in total hemoglobin concentration, blood oxygen saturation, water and lipid concentration, and tissue scattering. Blood flow in breast tumors, on the other hand, is a potentially important physiological quantity that has not as yet been accessed by the optical method. In this Letter we report what we believe to be the first diffuse optical measurements of blood flow in breast tumors. The measurements were carried out with a hand-held optical probe that was manually scanned over the tumor-bearing breast in a manner similar to the DOS approach of Jakubowski *et al.*⁷ Increased blood flow was observed in tumor regions relative to healthy tissue, and control subjects did not exhibit significant blood flow heterogeneity.

Blood flow in breast cancer is an important quantity to monitor, in part because it provides functional contrast complementary to tumor morphology. As such there have been numerous investigations of blood flow in breast by use of PET,⁸⁻¹⁰ color and power Doppler ultrasound,¹¹⁻¹³ and MRI.¹⁴ Clinical assessment of the ultrasound technique is ambiguous, because the methods are biased toward larger vessels and because of low signal-to-noise contrast. PET studies have been limited but have shown that blood flow tends to increase in malignant tumors. Both PET and MRI, however, have limitations due to cost and throughput issues associated with large instrumentation. The hand-held diffuse optical probes reported herein are portable, inexpensive, and offer robust rapid signals that can be repetitively obtained. Furthermore, the eventual combination of diffuse correlation spectroscopy for measurement of

blood flow with DOS, and for measurement of blood oxygenation and total hemoglobin concentration, may facilitate estimation of tumor oxygen metabolism.¹⁵⁻¹⁷

We recruited five patients with tumors and two healthy subjects. The measurements were carried out at the Hospital of University of Pennsylvania and were approved by the Internal Review Board. Subjects were asked to lay back in the supine position, thus flattening the breast and increasing tumor accessibility. An experienced researcher marked the tumor position and its extent on a transparency paper with grid and then scanned the hand-held probe shown in Fig. 1(a) in 1 cm increments along the horizontal and vertical directions across the tumor. Two scan directions were used to check for repeatability and ensure observed variations were not due to changes in the probe pressure. In healthy volunteers, an arbitrary region was drawn as the tumor site and the measurement was taken by scanning across that region, thereby providing information about blood flow heterogeneity in normal breast tissue. Average optical properties needed for analysis were obtained from separate DOS measurements of the same patients.⁶

Details of the instrument are described elsewhere.¹⁵ Briefly, a long coherence laser (Crysta Laser, Reno, Nevada) operating in continuous-wave mode at 785 nm was coupled to a 1×4 optical switch (Dicon, Richmond, California) and used to serially switch between four source positions. Four fast photon-counting avalanche photodiodes (Perkin-Elmer, Vudreuil-Dorion, Quebec, Canada) coupled to four single-mode fibers were used to detect the intensity fluctuations of the diffusing light in re-emission. The TTL output of the photodetector was fed to a four-channel custom correlator board (Correlator.Com, Bridgewater, New Jersey), and the resulting temporal intensity autocorrelation functions were re-

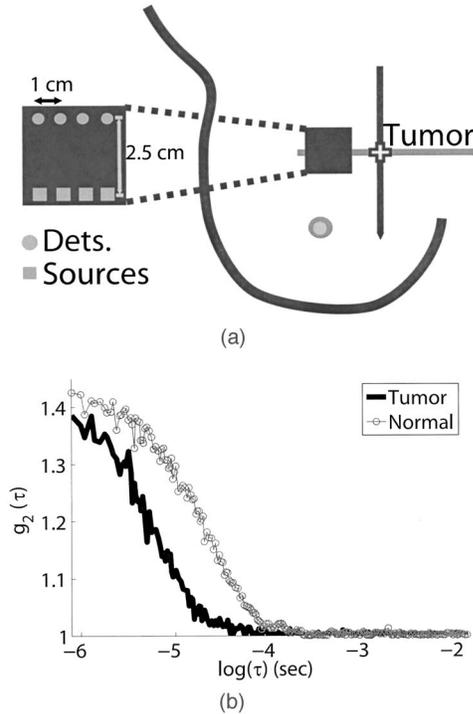


Fig. 1. (a) Hand-held probe with four source–detector pairs scanned horizontally and vertically in 1 cm increments spanning the estimated tumor region as well as the surrounding healthy tissue. (b) Temporal autocorrelation curves measured in the tumor (dark) and healthy (light) tissues of a patient. Faster decay corresponds to increased blood flow.

corded by a computer. A complete set of data was acquired every 6 s, and five such sets were acquired at each position. For this study, the four source–detector positions directly across from one another (i.e., with separation of 2.5 cm) were used at each scan position. The resultant autocorrelation functions were then fitted to a solution of the correlation diffusion equation^{15,18–20} to derive an index proportional to the tissue blood flow. In particular, the temporal decay rate of the autocorrelation function is quantitatively related to the motions of blood cells in underlying tissues. Tissue blood flow, derived from these effective decay rates were normalized to the mean value of the measurements of healthy tissue, and its standard deviation reported as the error bar. We therefore report the averaged relative blood flow (% rBF) at each position.

Figure 1(b) shows two autocorrelation curves from one patient. When blood flow increases, the temporal autocorrelation function decays more rapidly, reflecting the fact that blood flow is larger in the tumor region. Figure 2 shows horizontal and vertical profiles from one malignant tumor and one healthy breast. Very little variation is observable in healthy breast. However, the blood flow clearly increased in both scan directions as the probe crossed over the tumor. Furthermore, during acquisition, utmost care was taken to apply pressure evenly at each position on the tissue minimizing compression artifacts. Thus, the observed contrast is very likely due to the tumor and not the natural heterogeneity of the breast.

To compare the blood flow changes across tumor types, we tabulated the mean (\pm standard deviation) rBF within the estimated tumor region. Table 1 shows the distribution of rBF values for all subjects. Three groups are apparent from the data: (1) a group with very little heterogeneity, i.e., the healthy breasts (2.7% variation); (2) a group wherein blood flow increased to 230% of healthy tissue, i.e., malignant tumors; and (3) a group wherein a moderate increase to 153% over healthy tissue is observed, i.e., benign tumors. The contributions of normal tissue, located between the tumor and the tissue surface, to the signals can lead to underestimates of the contrast. In the future it should be possible to separate the contributions of superficial layers from underlying tumor tissues and thus improve contrast. Although the power of the statistics of this study is not enough to conclusively claim differentiation, we note that these results are in qualitative agreement with previous Doppler ultrasound and PET results,^{8–13}

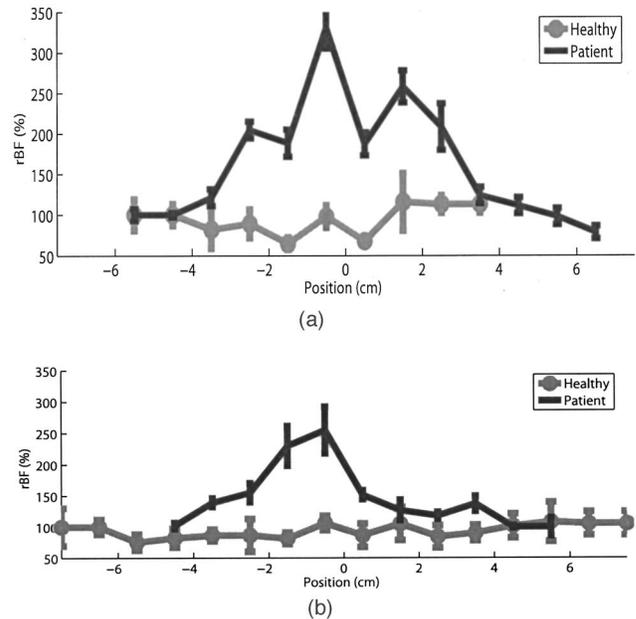


Fig. 2. Relative blood flow (rBF) scans from one patient with a malignant tumor and a healthy volunteer are shown for (a) horizontal and (b) vertical scans. Probe position is indicated relative to the expected tumor center.

Table 1. Tabulation of Relative Blood Flow (rBF) Measured in the Estimated Tumor Regions from all Subjects^a

ID	rBF (\pm std)	Type
1	100.5 \pm 13.4	Healthy
2	105 \pm 86	Healthy
3	144 \pm 21	Benign, calcification
4	163 \pm 26	Benign, calcification
5	184 \pm 16	Malignant
6	212 \pm 98	Malignant
7	298 \pm 51	Malignant

^aSubjects are grouped as healthy and with benign or malignant disease.

wherein $\sim 470\text{--}550\%$ increases in blood flow were reported in malignant tumors with smaller contrast in benign cases. In studies with larger populations, blood flow indices were used to differentiate up to nine different types of breast diseases.¹¹

These findings clearly demonstrate robust optical detection of blood flow changes in tumors. Further studies with more source–detector pairs are now underway to analyze potential partial volume effects that may influence our results. The palpable tumors are relatively superficial (~ 1 cm deep, ~ 2 cm diameter) and previous optical studies⁷ have shown that source–detector separations of 2.5 cm can probe these tumors in a repeatable manner. In the future, we will acquire data with a hybrid instrument¹⁵ that measures changes in blood oxygenation, total hemoglobin concentration and blood flow simultaneously and thus provides access to changes in tumor oxygen metabolism. These instruments are assembled on small clinical carts, and the study time is relatively short (~ 10 min). Therefore, it is feasible to acquire data at each patient visit in the triage area. We anticipate these methods will be clinically useful for therapy monitoring, for dose adjustment, and potentially for assessing efficacy of therapy.

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