Congruent MRI and Near-infrared Spectroscopy for Functional and Structural Imaging of Tumors

We present a combined near-infrared diffuse optical spectroscopy (DOS) and Magnetic Resonance Imaging (MRI) system for the study of animal model tumors. A combined broadband steady-state and frequency domain optical spectroscopy apparatus was integrated with the MRI. The physiological properties of tissue rendered by MRI, including vascular volume fraction and water, were compared with chromophore concentrations as determined from the parameters obtained by optical measurements. DOS measurements provided oxy-hemoglobin, deoxy-hemoglobin, and water concentration locally in tumors. A method for coregistration of the information obtained by both modalities was developed. Using Monte Carlo simulations, the optically sampled volume was superimposed on the MR images, illustrating which tissue structure was probed optically. Finally, two optical contrast agents, indocyanine green (ICG) and methylene blue (MB), were employed and their kinetics were measured by DOS system from different locations on the tumor and compared with Gd-DTPA enhancement maps obtained from MRI.

Key words: MRI, NIR, optical, spectroscopy.

Introduction

Modern image acquisition technology provides a multitude of non-invasive windows into the body. It not only allows us to view anatomical structures, such as visualizing bones, organs, and tumors in the body, but also provides the visualization of physiological, cellular, or molecular processes in living tissue as they take place in near-real time. Recently, there has been a great deal of interest in further improving the in vivo characterization of tumors by interrogating tissues with multiple simultaneous measurement techniques that provide complementary information about the state of the sample under investigation. Besides offering the possibility of complementary information, multi-modality techniques could also be used to improve the measurements done by either modality as well as providing cross validation measurements. Magnetic resonance imaging (MRI) and near-infrared diffuse optical spectroscopy (DOS) are two techniques that, when combined, provide complementary structural and functional information. MRI can be used to obtain detailed structural and metabolic information regarding tumors. On the other hand, DOS can provide local quantitative information regarding tumor composition and metabolism. A combined system consisting of MRI and DOS has the potential to enhance our understanding of the complex biological processes associated with tumor progression and response therapy.

Various MR imaging techniques have been used to quantify some of the physiologic properties of tissues such as fat/water, \( pO_2 \) and vascular volume fraction. The separation of fat and water has been achieved by utilizing their slightly different res-
onance frequencies. This fact was first exploited by Dixon to separate fat and water from two MR images encoded as in- and out-of phase with respect to water and fat (1), and later improved by Glover et al. (2). Tumors have hypoxic cells, which are known to resist to radiation and/or chemotherapy (3-4). One of the most promising MR techniques developed to quantify the tumor oxygenation and distinguish hypoxic regions is based on F-19 (5-12). Recently, dynamic Gd-DTPA enhanced MRI (DCE-MRI) has been applied extensively to study pO2 in tumors (13). At low pO2 values, which are more interesting biologically, the pO2 is linearly proportional to vascular volume fraction that can be obtained by the DCE-MRI. A two-compartment model described by Tofts (14) has been used in conjunction with Gd-DTPA and Gadomer-17 enhanced MRI to extract the vascular fraction volume (13,15-17).

Near-infrared (NIR) diffuse optical spectroscopy is promising method of obtaining new types of physiological information from tissue and has been employed to investigate muscle (21, 22), brain activation (23, 24), and assess physiological responses from normal and malignant breast tissue (25). Optical absorption (μa) and reduced scattering (μs') coefficients are direct measures of tissue biochemical composition and morphology and are true functional indicators of the composition of a tissue system. Optical absorption arises from the presence of specific biomolecules that absorb light at a particular wavelength. For near-infrared light (650-1000 nm), these biomolecules include hemoglobin (Hb) oxygenated-hemoglobin (HbO2), water (H2O) and fat. There is also an increased interest in the use of optical contrast agents for probing tissue functional characteristics. Non-invasive measurement of optical contrast agent dynamics in tumors after intravenous injection has been reported by many groups (30-32). Thus, an accurate, quantitative measurement of optical absorption at multiple wavelengths in the near infrared provides the means to determine the absolute concentrations of both endogenous and exogenous chromophores within tissue.

MRI is an excellent candidate as a complementary modality to NIR-DOS due to its excellent sensitivity, the detailed anatomical information it renders and the fact that it also employs non-ionizing radiation. The high resolution functional information obtained from MRI can be used for the validation and assessment of the optical measurements, while the anatomical information can be used to improve the reconstruction of optical parameters from the measurements. Although a number of investigations reported in the literature combine both modalities in the area of functional brain imaging (26-27), only a few reports are available for cancer studies (28-29).

In this study we present a congruent MRI and DOS instrumentation along with a method developed for co-registration of the data rendered by both modalities from an in vivo tumor model. Measurements were taken on subcutaneous tumors in rats periodically over an interval of 20 days. The oxy-hemoglobin, deoxy-hemoglobin and water concentration obtained from DOS are compared to water and blood vascular fraction information obtained from MRI. Two optical contrast agents, indocyanine green (ICG) and methylene blue (MB), were employed and their kinetics were measured by DOS system from different locations on the tumor and finally, compared with Gd-DTPA enhancement kinetics obtained from MRI.

Materials and Methods

MRI Instrumentation and Methodology

The MRI studies were performed with a homebuilt 3T scanner with a Marconi Medical, Inc. console. The bore diameter was 90cm and a birdcage type, small animal, transmit-receive RF coil was utilized. Due to the effects associated with the 3T magnetic field, the optical instruments were placed in a separate room, 20m away from the magnet bore. Optical fibers were used to conduct light from the sources to the tissue as well as to transfer collected light from tissue to detectors as depicted in Figure 1. An optical probe, which was designed to hold the source and detector optical fibers at a fixed separation, was placed inside the RF coil. The details of this probe and optical fibers are explained in the optical instrumentation section.

Two types of MRI images were obtained. First, T2-weighted images using a fast spin-echo (FSE) sequence with TR/TE = 3000/15 ms, echo train = 8, field of view (FOV) = 10.5 cm, Image-Matrix = 256 × 256 and 5mm in slice-thickness were acquired over the whole tumor for the anatomical information. T1-weighted dynamic acquisition was subsequently performed based on a fast 3-D gradient echo pulse sequence with TR/TE = 18/3.6 ms, flip-angle = 20°, FOV =10.5 cm, Image-matrix = 128 × 128 and 5mm in slice-thickness. In this acquisition, a sequence of 40 dynamic images with a total duration of about 16 min (δt = 24.1 sec.) was obtained. A bolus injection of Gd-DTPA (molecular weight <1kD, 0.1 mmol/kg) was administered after the first
4 images (baselines) in this T1-weighted acquisition. The Gd-DTPA induced enhancement kinetics from the tumor were measured by subtracting the average intensity of the 4 baselines from each of the subsequent dynamic images following the Gd-DTPA bolus, based on the assumption that the enhancement is proportional to the Gd-DTPA concentration (15, 33, 34). The vascular volume (Vb) was derived from pharmacokinetic modeling analysis of the intratumor kinetics of MR contrast agents (15). After vascular and interstitial contributions to the recorded signal were separated, the derived parameters were used to characterize the vascular volume quantitatively (35). Tissues were classified as viable and edematous based on their different enhancement kinetics, as illustrated in Figure 2. The detailed explanation of this method was provided by Su et al. in this current issue.

For optical measurements, a combined frequency-domain (FD) and a steady-state (SS) system were used. This combined system allows for the determination of the broadband absorption spectrum of the tissue across the entire range of the interest ~650-1000nm and it has been previously described in detail (20). The FD system is based on a network analyzer (HP 8753C), that allows for modulating the intensity of laser diodes as well as measuring the amplitude and phase changes of intensity modulated light propagating in the tissue. Five laser diodes at varying wavelengths of 674, 800, 849, 898 and 915 nm were used, and were modulated from 50 to 601 MHz sweeping a total of 233 frequencies. An avalanche photodiode module (Hamamatsu APD C556P-56045-03) was used to detect the optical signal collected from the tissue. On the other hand, the SS instrument was utilizing a tungsten-halogen light source (Ocean Optics LS-1) to illuminate the tissue and a fiber optic spectrometer (Ocean Optics S2000) to obtain the reflectance spectrum of the tissue.

For SS measurements 600 µm core diameter step index fibers (OZ Optics QMMF-5X-IRVIS-600/630-3-40) used for both source and detector fibers. Although the SS measurements were not affected significantly by the usage of 20m source and detector fibers, FD measurements were influenced from the modal dispersion of the step index fibers due to the modulated light signal used in FD method. To overcome this problem, a commercially available 100 µm core diameter gradient index fiber (OZ Optics MMJ-3X-IRVIS-100/140-3-40) used as the source fiber, while a custom 600 µm core diameter gradient index fiber produced specifically for this application (Oxford Electronics) used as the detector fiber. The cladding diameter was 140 µm and 1.1 mm for the source fiber and detector fiber, respectively. Both optical fibers were protected by 3mm furcation tubing and passed through the RF waveguides located in the penetration panel of the RF shielded MR scanner room. To be able to hold them on the sample inside the animal RF coil, a probe made of Delrin was prepared. The probe head was a cylinder and one-inch in diameter. The source and detector fibers were inserted into the drilled holes and fixed in place flush with the probe head with epoxy.

The method used to determine the optical properties of the measurement volume includes the following steps, which are explained previously in detail (20). First, µa(λ) and µs′(λ) are obtained at the laser diode wavelengths from the fit of the diffusion solution to the calibrated phase and amplitude. For the FD measurements, amplitude and phase were calibrated using a silicone phantom with previously characterized optical properties (19). For the SS measurements, an integrating sphere was used to calibrate the spectral instrument response. As numerous groups of researches have observed (36-38), the particle size distribution of scatterers (0.1-10µm) in biological media and tissue phantoms tends to have a smooth near infrared wavelength dependence that is well described by a power function of the form µs′(λ) = A · λ^B. As a result, measuring several µs′(λ) values at the laser wavelengths allows one to fit those numbers to a simple function of wavelength and to obtain good estimates of µa′(λ) at all other wavelengths needed. The µa(λ) and µs′(λ) values at the laser wavelengths obtained from FD measurements are also used to calibrate the broadband reflectance spectrum R(λ) obtained from SS measurements, again using diffusion theory. The last step is to determine the broadband absorption spectra, µa(λ), from the broadband absolute reflectance spectra R(λ) and the broadband µs′(λ) spectrum, using the diffusion solution a third time.

To determine physiological properties, we assume that the optical absorption measured at a given wavelength is due to the sum of the absorption provided by the principal chromophores within tissue at the wavelengths probed. These chromophores consist of simply hemoglobin (Hb), oxygenated hemoglobin (HbO2), water (H2O) and fat. Therefore, a system with four principal chromophores equations of the form

\[
\mu_a(\lambda) = \mu_{Hb}(\lambda) + \mu_{HbO2}(\lambda) + \mu_{H2O}(\lambda) + \mu_{fat}(\lambda)
\]

\[
\mu_{s'2}(\lambda) = \mu_{Hb}(\lambda) + \mu_{HbO2}(\lambda) + \mu_{H2O}(\lambda) + \mu_{fat}(\lambda)
\]

\[
\mu_{s'}(\lambda) = \mu_{Hb}(\lambda) + \mu_{HbO2}(\lambda) + \mu_{H2O}(\lambda) + \mu_{fat}(\lambda)
\]

\[
\mu_a(\lambda) = \mu_{Hb}(\lambda) + \mu_{HbO2}(\lambda) + \mu_{H2O}(\lambda) + \mu_{fat}(\lambda)
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\[
\mu_{a}(\lambda) = \mu_{Hb}(\lambda) + \mu_{HbO2}(\lambda) + \mu_{H2O}(\lambda) + \mu_{fat}(\lambda)
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\[
\mu_{s'}(\lambda) = \mu_{Hb}(\lambda) + \mu_{HbO2}(\lambda) + \mu_{H2O}(\lambda) + \mu_{fat}(\lambda)
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\mu_{s'}(\lambda) = \mu_{Hb}(\lambda) + \mu_{HbO2}(\lambda) + \mu_{H2O}(\lambda) + \mu_{fat}(\lambda)
\]

\[
\mu_{a}(\lambda) = \mu_{Hb}(\lambda) + \mu_{HbO2}(\lambda) + \mu_{H2O}(\lambda) + \mu_{fat}(\lambda)
\]

\[
\mu_{a}(\lambda) = \mu_{Hb}(\lambda) + \mu_{HbO2}(\lambda) + \mu_{H2O}(\lambda) + \mu_{fat}(\lambda)
\]

\[
\mu_{s'}(\lambda) = \mu_{Hb}(\lambda) + \mu_{HbO2}(\lambda) + \mu_{H2O}(\lambda) + \mu_{fat}(\lambda)
\]

\[
\mu_{a}(\lambda) = \mu_{Hb}(\lambda) + \mu_{HbO2}(\lambda) + \mu_{H2O}(\lambda) + \mu_{fat}(\lambda)
\]
\[ \mu_a^2 = \epsilon_{\text{Hb}}^2 [\text{Hb}] + \epsilon_{\text{HbO}_2}^2 [\text{HbO}_2] + \epsilon_{\text{H}_2\text{O}}^2 [\text{H}_2\text{O}] + \epsilon_{\text{fat}}^2 [\text{fat}] \]

is constructed for each wavelength for which measurements of \( \mu_a(\lambda) \) available. In these equations \( \epsilon \text{[chromophore]} \) represents the extinction coefficient (in units of \( \text{mm}^2/\text{mole} \)) of a given chromophore at wavelength \( \lambda \) and [Hb], [HbO\(_2\)], [H\(_2\)O] and [fat] are, respectively, the concentration of Hb, oxygenated Hb, deoxygenated Hb and fat (mol/mm\(^3\)) in the tissue under the study. Using a matrix representation of these linear equations, the concentrations of the four unknowns can be calculated (18). Therefore, by using the combined SS and FD system, the concentration of each chromophore can be obtained for the measurement volume across the entire range of the interest ~650-1000nm.

**Measurements and Co-registration**

The experiments were performed on ten female Fisher-344 rats bearing R3230 AC adenocarcinoma tumor model. The tumor was implanted by injecting 0.5mL of minced tumor cell suspension subcutaneously into the left thigh of the rat. The imaging experiments were initiated when tumor sizes reached 1 cm in diameter and repeated periodically until tumors reached a maximum size of 3 cm in diameter. Each rat was measured every 3-5 days over a period of 20 days. All procedure followed a protocol approved by the Institutional Animal Care and Use Committee of the University of California, Irvine.

The imaging procedure includes four steps: (a) MRI guided positioning of the optical probe head on the tumor, (b) T\(_2\)-weighted anatomic MRI acquisition and optical (FD-SS) data acquisition, (c) T\(_1\)-weighted dynamic acquisitions along with optical (FD-SS) data acquisition, and (d) optical instrumentation calibration, Figure 3.

After this first step, T\(_2\)-weighted anatomic MR images covering the whole tumor were acquired along with the FD and SS optical measurements. Optical data was acquired 3 times during the acquisition of the T\(_2\)-weighted anatomic images. In the third step, 40 T\(_1\)-weighted dynamic images covering about 16 min were acquired. Three additional FD and SS optical measurements were taken during this dynamic acquisition. Finally, the calibration measurements for optical FD and SS measurement were acquired and imaging studies were completed.

The tumor enhancement kinetics measured from the dynamic T\(_1\)-weighted were analyzed on a pixel-by-pixel basis by using a 2-compartmental model (15) to derive the vascular volume related parameter (V\(_b\)) map. Then, a Gd-DTPA enhanced map was produced to separate the viable and non-viable voxels in the measurement volume. This enhancement map was obtained by subtracting the baseline image from the fourth T\(_1\)-weighted image acquired after the administration of Gd-DTPA (Fig. 2). The viable and non-viable pixels from this enhancement map were separated by applying threshold segmentation. The pixels with low or no enhancement showed higher signal intensity in the T\(_2\)-weighted images. Typically, the pixels with high signal in the T\(_2\)-weighted images have higher water content and, according to our previous experience with this tumor model, are correlated with edema. Therefore, the T\(_2\)-weighted images along with the enhancement map were used to compare the water content information obtained from MR and optical spectroscopy measurements.
The combined frequency-domain (FF) and steady-state (SS) optical measurements provided the absorption spectrum measured on the rat tumor and thus, the tissue chromophore (Hb, HbO₂, H₂O and fat) content. Unlike MRI that can provide a cross-sectional image of the tumor, optical spectroscopy has a limited probing depth due to attenuation and scattering nature of the tissue. To be able to create a map representing the optically probed region, Monte Carlo (MC) simulations based on measured average transport parameters were utilized (39, 40). A 3D mesh structure representing the tumor volume under the probe was constructed for this purpose. The contribution of each pixel in this 3D mesh to the collected optical signal is not the same and the constructed weighted MC map describes the probability for a detected photon that have traveled through a given pixel of this 3D mesh. The input parameters used in the generation of the MC maps included the modulation frequency, source-detector separation and the measured optical coefficients \( \mu_a, \mu_s' \). For the purposes of this investigation, we determined that the frequency/wavelength dependent variations in interrogated tissue volumes were not significant for optical properties between 650nm to 1000 nm and for the modulation frequency range used (50-601 MHz). Thus, the maps were generated using the average optical properties and modulation frequency (300 MHz), Figure 6b.

After superpositioning of the MC maps over the MR images with the help of markers, the weighted \( V_b \) maps were obtained by multiplying the MC maps with the \( V_b \) maps obtained from the dynamic MR studies on a pixel-by-pixel basis. After the multiplication, the weighted average \( V_b \) value was found for each tumor at the different time points. This average \( V_b \) value was compared with the oxygen saturation (SO₂) value obtained from optical spectroscopy, the ratio of HbO₂ to the sum of Hb and HbO₂. In addition to this, a ROI was obtained from these weighted Monte Carlo maps by applying a threshold approach. The ROI was superimposed onto the corresponding MRI enhancement map to determine the non-viable pixel fraction within the optically probed volume as bounded by MC-ROI. Then, the non-viable pixel fraction obtained from the corresponding enhancement maps as enclosed by this ROI was compared with the water content information obtained from the optical spectroscopy measurements.

Finally, concentration vs. time of indocyanine green (ICG) and methylene blue (MB) were measured in tumor tissue proceeding bolus dose administration. Only steady-state (SS) broadband reflectance measurement with 600 msec integration time was used for optical contrast agent studies. Contrast agent bolus injections of 55 mg/kg, 10 mg/kg and 7.5 mg/kg for Gd-DTPA, MB and ICG, respectively, were administered to the rats via the tail vein. The agents were combined with a saline flush such that the total fluid administered was 1.5 mL (≈10% of the total blood volume). The measurements were begun approximately 10 seconds before injection, and continued for approximately 10 minutes post-injection. The injections were performed in series with Gd-DTPA first, then MB, and finally ICG approximately 15 minutes after the MB injection. The optical measurements were recorded from different regions of the tumor with the guidance of MR enhancement images. The entire sequence of optical measurements was performed without movement of the fiber probe allowing for reliable comparisons of results from the same tissue volume.

**Results**

The optical measurements were taken totally six times before and after the Gd-DTPA bolus injection. The six measurements were averaged standard deviation of all measurements were calculated. Average standard deviation for optical measurements of chromophore contents was around 5%. There were no consistent differences in optical data taken before and after measurements; therefore, the MRI contrast agent did not appear to perturb the absorption and scattering events of the light, either directly or as a consequence of blood dilution.

Figure 5 shows a typical \( \mu_a \) spectrum measured on the rat tumor, as computed based on the frequency-domain and steady-state measurements explained in methods section. The fit of the chromophore spectra (Hb, HbO₂, H₂O and constant background absorption) to the \( \mu_a \) spectrum allows for the determination of the concentrations. Although our DOS instrument also has the ability to determine lipid concentrations the tumor tissues measured contained insignificant amounts of fat and did not necessitate the use of the fat spectrum in the chromophore fit. The background absorption was used to account for chromophores with flat spectra.

![Figure 5](image_url)

**Figure 5:** Solid line is \( \mu_a \) tumor spectrum measured optically with DOS instrument. Dashed line is fit of Hb, HbO₂, H₂O, and baseline absorption spectra to measured \( \mu_a \) spectrum.
in the near-infrared region and systematic instrumental errors. Figure 5 illustrates that the fit is excellent. The various features of Hb and H₂O absorption are clearly visible: high absorption of Hb at 650 nm (peak at 555 nm), peak of Hb at 758 nm, and peak absorption of H₂O at 978 nm.

To effectively compare the Hb, HbO₂, H₂O concentrations to MRI data, it is crucial to define which tissue region is probed optically. As explained in the Methods section, we performed Monte Carlo (MC) simulations for that purpose. Figure 6a shows a typical example of a superposition of the MC map over a MR image. Figure 6c shows a vascular fractional volume (Vb) map of a tumor as derived from pharmacokinetic modeling analysis of the intratumor kinetics of Gd-DTPA. This Vb map was multiplied with the MC map, Figure 6d, on a pixel by pixel basis which was obtained from the simulations to obtain the weighted Vb map, Figure 6e.

The weighted average Vb value was found for each measurement and compared with oxygen saturation (SO₂) obtained from DOS. Also, the non-viable pixel fraction obtained from MR measurements was compared with the water content values obtained from DOS as explained in method section. Figure 7 shows the T₂-weighted, and T₁-weighted enhancement images of a typical example of “viable” and “edematous” tissue. Viable tissue is visually characterized by average or high signal (bright regions) of Gd-DTPA on the enhancement image, and low signal (dark regions) in the T₂ weighted image. The enhancement corresponding to the viable region is above a certain threshold value, which signifies a sufficient blood flow to the considered region. On the other hand, the enhancement value corresponding to the edematous region is below a certain threshold while the T₂ signal for the corresponding region is relatively high. Edematous tissue is visually characterized by average or low signal (dark regions) of Gd-DTPA on the enhancement image, and relatively high signal (bright regions) in the T₂ weighted image.

Figure 6: An example of (a) an enhancement image and the overlapped MC map, (b) a MC map for a tissue with μₐ = 0.05 mm⁻¹ and μₐ′ = 1.70 mm⁻¹ at modulation frequency of 300 MHz (c) a Vb map for a tumor (d) the MC map for that tumor, and (e) the weighted Vb map (Vb × MC).

Preliminary results including 23 measurements demonstrate classification of three tissue types: “viable”, “edematous” and “necrotic/hypoxic”. Figure 8 shows the percentage of nonviable pixels in the optically sampled volume versus water content information obtained from DOS. Based on the non-viable pixel percentage obtained from MRI, tissue types can be grouped in to viable (< 75%) and non-viable (> 75%) type. The viable tissue type also showed relatively high Vb value (0.194 ± 0.142), while the non-viable tissue type showed low Vb values (< 0.04), Figure 9. The non-viable tissue data were clustered in to two with respect to their water content information obtained from DOS. The measurements performed on the “edematous” tissue separated clearly from all other measurements because of the high, relative water concentration measured by both modalities, which was also expected. For the edematous tissue, the
average non-viable pixel percentage was 94.4 ± 0.142% (MRI), while the average H2O content obtained by DOS was 89.9 ± 7.2M. On the other hand, the second type of tissue that exhibits very low water concentration in the DOS measurements called "necrotic/hypoxic" tissue. Although "viable" and "necrotic/hypoxic" tissue types were clustered together (23 M to 36 M) based on water content obtained from DOS, separation occurred between these two types of tissue as values decrease in SO2, Figure 9. Necrotic tissue showed significantly lower tissue SO2 (45.3 ± 9.8 %) compared to viable (59.8 ±6.3%). These results were consistent with expected physiological differences.

For viable tissues, we believe that our diffusion model holds, even if the source detector separation used here is relatively small (5.7 mm). Kienle et al. demonstrated indeed that retrieval of $\mu_a$ with $\mu'_s=1$, at a single distance of 6 mm and a modulation frequency of 195 MHz resulted in an error less that 10% when the $\mu_a$ value to be determined was less than 0.02 mm$^{-1}$ (41). We also performed a validation study on a phantom at a range of source/detector separations to test the limits of our instrument’s ability to extract the correct optical coefficients and found similar errors for a distance of 5.7 mm. Moreover, the use of the broadband absorption spectrum increases accuracy in the recovery of chromophore concentrations.

However, the values of water concentration obtained by DOS in edematous tissue exceed physical plausibility. This problem is most likely a combination of two factors. First, the edematous case, as viewed on MRI, is comprised of a low scattering mixture consisting of mostly water; such a tissue type may easily exceed the limits of diffusion theory, especially at the short source/detector separation used (5.7 mm). Second, the errors can also be explained by the actual structure of such tissues, which are neglected in our optical model. The T2 MR image of edema shows that these cases should be considered at least as a two-layer structure. The first layer, typically 1 mm thick or less, is composed principally of the skin. The second layer is the edema itself, characterized by a high water concentration and hence low scattering. In such a case, previous investigations have shown that the diffusion model, assuming a semi-infinite homogeneous case, is usually inaccurate (47, 48). Qualitatively, the optical measurements provide the correct trend, i.e. high water concentration, but the values are quantitatively inaccurate.
Finally, we present the time course measurements of optical contrast agents MB and ICG taken from different regions of the tumor. Figure 10 shows an example of time-course measurements of MB, ICG and Gd-DTPA from the same region of a tumor. The time-dilution curve for MB demonstrates very rapid extravasation of the agent from the vascular compartment into the interstitial space, with a single-exponential half-life of approximately 15 sec. In contrast, ICG shows a much slower time course, with a single-exponential half-life of approximately 520 sec. This high value can be attributed to albumin-bound ICG’s high effective molecular weight (>55 kD) and its retention in the vascular compartment (30). Figure 11 is a plot of MB dilution for Gd-DTPA MRI enhanced and non-enhanced regions of a tumor. In these preliminary results, the non-enhanced tumor regions show both a significant decrease in absolute intensity, as well as slower dilution kinetics. It is possible that measurements such as these could potentially increase sensitivity and specificity for optical detection of tumors and aid in characterization of tumor vascular state.

Conclusion

In this work, we present a hybrid MRI and broadband diffuse optical spectroscopy (DOS) instrument. A method for coregistering of the information obtained from both modalities was developed. The physiological parameters rendered from both modalities on subcutaneous adenocarcinoma tumors in a rat model were obtained and compared. To our knowledge, not only a few studies using DOS on animal model tumors (42-45), but also only one study comparing DOS data with T2-weighted MRI data (46) have been reported. Further studies required for better assessment of the physiological parameters obtained by DOS and comparison of these with the parameters obtained from MRI. The combined MRI/DOS system has the potential to monitor chemotherapy and other cancer treatments on a tumor model. Therefore, the future studies will also include non-invasive evaluation of the efficacy of a treatment method and will focus on advancing the optical instrumentation by adding tomographic capabilities.

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