Ongoing research and investigation into Image-Guided Near-Infrared Spectral Tomography is aimed at developing it for use in the detection and characterization of known breast cancer because of its unique ability to map hemoglobin, water, and lipid content in tissue. The method uses measurements of light transmitted through the breast at multiple wavelengths to quantify the spectral absorption and elastic scattering properties of tissue.

Breast cancers have been shown to have higher hemoglobin and water content and lower lipid fraction relative to normal parenchyma [1-5]. Because of its modest cost and use of non-ionizing radiation, the technique can be applied to monitor tissue without safety concerns, and integrates with magnetic resonance (MR) breast imaging. Introduction of near-infrared spectroscopy (NIRS) into an existing 3T Achieva MR scanner is demonstrated and representative case studies are presented that show results for intrinsic tumor spectroscopy.

In addition to its potential in breast screening [6], NIRS may hold promise in monitoring the effectiveness of chemotherapy [7]. Cerussi et al. [8] showed that breast monitoring with near infrared light was able to predict chemotherapy response in 11 patients within the first week of treatment. In particular, the absolute concentration of total hemoglobin in tumors and the relative differences in deoxyhemoglobin and water in tumors versus normal tissue demonstrated significant separation of treatment responders from non-responders among the women enrolled in the study.

Cost-effectiveness studies of this approach indicate that the technology should be beneficial in the individualization of neoadjuvant chemotherapy, as long as the initial treatment is less than 90% effective and the cure rate can be increased by as little as 1% through a change to an alternate therapy [9]. Admittedly, optical/NIRS imaging of the breast has exhibited limited success in the screening and diagnostic settings. In several clinical trials, improvements in specificity have been reported because of better lesion characterization [10, 11]. Unfortunately, optical mammography has been unable to characterize small lesions (less than 6 mm) when used alone because of its spatial resolution limitations, which are caused by the excessive light scatter in all tissue.

Indeed, both of the larger breast optical imaging studies described in the literature have either noted the poorer characterization of lesions less than 6 mm [11], or excluded lesions smaller than 8 mm altogether [10]. As a result, the focus on breast cancer screening with NIRS has not led to a technology that has gained clinical acceptance for screening. However, alternative applications continue to be explored and carefully evaluated in order to identify the best possible opportunities for NIRS in breast health care [12].

One promising avenue for NIRS is to focus on its spectroscopic strengths in characterizing tissue without requiring high spatial resolution. Image-guided NIRS makes the strategy possible by using the spatial template of the MR image upon which localized spectroscopy is superimposed. This concept was initially demonstrated for individual wavelength imaging in the breast some 10 years ago [13, 14].

A more recent version of the approach has exploited multi-spectral measurements to characterize the fibro-fatty constituents within the breast [15, 16]. High-resolution spatial guidance from X-ray or MR has demonstrated an improvement in both the spatial resolution and quantification accuracy of NIRS [17-19]. Initial breast cancer images have recently been reported with the approach [20, 21]. The clinical performance of these coregistered multi-modality methods has yet to be fully evaluated.
in a clinical trial. However, the phantom and clinical case studies shown to date clearly indicate that MR-guided NIRS will improve upon the results obtained with stand-alone NIRS imaging.

This paper briefly summarizes the MR-guided NIRS system research developments that have taken place at Dartmouth Hitchcock Medical Center in collaboration with Philips Research over the last several years. Several case studies of recent study results are presented to illustrate the promise of multi-modality NIRS, not only in terms of improving the performance of optical breast imaging alone, but also in augmenting tumor detection, characterization and monitoring with breast MR.

Methods

Instrumentation
The optical instrumentation, shown in Figure 1, uses 16 fibers that sequentially deliver light from multiple sources (six separate diode lasers covering the 660–850 nm range) and channel the collected light to a bank of photomultiplier tube (PMT) detectors. Light from the six individual diode lasers is delivered through the fibers to the breast, with an intensity modulation frequency of 100 MHz. The transmitted signals are detected by PMTs matched to each fiber.

The resulting signal is mixed down to low frequency, after which its amplitude and phase are measured through A/D capture at each detector. The phase shift of the 100 MHz light is a direct measure of the scattering path-length that the light has traveled through the breast, thus allowing separation of the effects of scatter from absorption using a diffusion-based spectral estimation process.

The fiber optic lines extending from the breast to the data acquisition hardware are 13 meters long, and are non-magnetic. The breast interface has been integrated within the plates of an MR breast RF coil, allowing the NIRS data to be recorded while the scanner is in operation. The patient is positioned prone inside the bore of the magnet (Philips Achieva 3T X-series) with the breast pendant into the fiber array interface.

While early work was performed with the fibers in a circular geometry, as presented here, a more advanced version of the system conforms to the standard biopsy plates to facilitate clinical workflow. The current design, consisting of 16 fibers, is a prototype that provides one coronal slice of optical measurements. It is possible to incorporate more fibers for multi-slice data acquisition as is routinely performed in standalone NIRS systems.

MRI was used to acquire anatomical features that were integrated within the NIRS image reconstruction procedure [20]. Specifically, 3D T1-weighted Spin Echo (TR/TE = 900/10, flip angle = 18°) MR images were recorded to separate adipose and fibroglandular tissue, which are expected to have distinct optical properties [16]. Regions of interest, determined by Dynamic Contrast Enhanced MR (DCE-MR), were obtained by injecting a bolus of contrast agent (Magnavist) intravenously. A series of T1-W volume images (TR/TE = 10/6, flip angle 20°) were then acquired after each minute, beginning 40 seconds post-injection.

Image reconstruction
Tissue absorption and scattering characteristics were determined by simultaneously reconstructing the NIRS data at all wavelengths. Light propagation was modeled by the diffusion equation. This accurately describes signal propagation in tissue when scattering dominates over absorption and when source-detector distances are larger than a few scattering lengths [22].

To form a spectroscopic set of images, a model based estimation algorithm is used that minimizes the mismatch between the NIR data collected and the quantities computed through the diffusion equation [23, 24]. The method also recovers the tissue scattering spectrum in...
Results

Image guided versus non image guided NIRS

A representative example of NIRS image improvement with MR guidance is illustrated in Figure 2. Here a patient, who was an eventual non-responder to neoadjuvant chemotherapy, was examined on the same day before treatment with a stand-alone (Figure 2a) versus an image guided NIRS system (Figure 2b). Image guidance leads to a dramatic improvement in contrast localization and contrast delineation of background tissue types that is not evident in the stand-alone diffuse image.

Patients

In this case-study report, imaging results from three patients are described. The patients were evaluated during various stages of neoadjuvant chemotherapy for breast cancer treatment. All subjects provided informed consent. They were then imaged according to the research study protocols approved by the Institutional Review Board at Dartmouth Hitchcock Medical Center.

Individual cancer imaging

Three subjects undergoing neoadjuvant chemotherapy were imaged during treatment. These subjects had invasive ductal carcinomas (IDCs) confirmed via biopsy. These examples
show classic contrasts, where the cancer had higher hemoglobin and water contents because of the increased vascularity expected in tumors. Tumors also typically have a higher cellular packing density because of this vascularity, but scattering contrast was not observed in the non-responding cancer case presented below. Imaging results are shown in Figure 3 and Figure 4.

Subject 1
The subject, a 36 year old woman at the time of imaging, had a 3 cm IDC and DCIS lesion in the right breast. Imaging was performed one day after the first cycle of treatment. Results show a decrease in hemoglobin of 20 µM in the region of interest, compared to near 30 µM in the background. Interestingly, the fibroglandular tissue presented lowered hemoglobin that could be due to the large extent of collagen evident in the corresponding mastectomy slice obtained after surgery.

Oxygen saturation in the region was 60% compared to nearly 75% in the background, and water concentration was closer to 40%, compared to 60% in the background. Scattering resulted in an increased particle density near $3.5 \times 10^{16}$, and particle size was homogeneous near 1 µm across the image plane. The reading radiologist reported a suspicious lesion appearing in the DCE-MR exam that was not apparent on previous MR scans.

Pathology performed seven weeks later revealed a complete response to chemotherapy with no viable tumor remaining. However, there was residual scar tissue in this location (see Figure 3d) that likely contributed to the lower quantities of hemoglobin, oxygenated hemoglobin, and water as compared to the background. This case is an interesting demonstration of where the NIRS findings could have significant diagnostic potential to eliminate the false positive reading from the MR exam that would have resulted in an additional MR-guided biopsy in most cases.

Subject 2
The subject, a 51 year old woman at the time of imaging, had a 7 cm IDC in her left breast. Imaging was performed seven days prior to the first cycle of chemotherapy. MR-NIRS results showed an increase in hemoglobin to greater than 180 µM compared to 40 µM in the background. Hemoglobin oxygenation was 80%, slightly lower than the 85% in the background. Water was elevated to 95% from near 60% in the background. A slight increase in effective scattering particle size to 0.95 µm compared to 0.95 µm as well as a lower particle number density, around $0.5 \times 10^{16}$ compared to nearly $1 \times 10^{16}$ in the background. It is important to note that in this case the optical system was not able to fully sample the tumor volume. Instead, a plane was imaged near the extreme posterior aspect of the cancer.

Figure 3a. MR-NIR images overlaid over the T1-W MR slice in the plane of the optical fibers. There is an increase in particle number density, but no change in particle size.
Figure 3b. The T1-W MR slice in the plane of the optical fibers taken two months before surgical mastectomy of a patient who fully responded to chemotherapy. These images show a decrease in hemoglobin, oxygen saturation, and water in the region of interest with respect to the background.
Figure 3c. DCE-MR identifies a suspicious region spatially correlating to a non-fatty area in the T1-W image.
Figure 3d. Pathology showed no viable tumor.
response to treatment. Water diminished in the anterior lesion from about 42% to 38%, most likely because of the reduction in functional vascular tissue in the tumor. Oxygen saturation also decreased, likely because of destruction of functioning tumor vasculature, which restricted tumor perfusion.

**Discussion**

This study presents MR-guided NIRS for delivery of multi-modality breast exams. The ability to obtain spectroscopic information on both the absorbers present in tissue, and the effective scattering particles, is unique and has the potential to contribute pertinent diagnostic information. The MR-guided recovery of NIRS parameters in Subject 1 was significant because they allowed identification of lesion features that were not suggestive of cancer.

Ultimately, analysis of the tissue removed during surgery confirmed that the lesion, which was enhanced by DCE-MR, was not malignant but a fibrotic scar left after neoadjuvant chemotherapy. While this case was not in need of highly sensitive diagnostic accuracy, it was complex and the additional characterization of the breast would have helped the attending physicians recommend the best treatment option (for example, of mastectomy or not).

Subject 3 represents a case where tracking the response to chemotherapy was important because a significant change in response to neoadjuvant chemotherapy occurred in a breast which presented with multiple lesions. Following each of these lesions with biopsy is not practical in many circumstances. Hence, the additional...
spectroscopic data can be used to inform the case management [29].

As enrollment in the study presented here is ongoing, a more comprehensive summary data will be published in the future. From a system design and performance evaluation perspective, the NIRS components have little impact on MR scanner performance and exam administration. Future versions of the NIRS breast interface will have the optical fibers integrated into biopsy plates, allowing more space for positioning of the breast in the fiber array, which is of particular interest in the ongoing collaboration between Dartmouth Hitchcock Medical Center and Philips Research in Hamburg.

Acknowledgments
This research work has been funded by the National Institutes of Health grants RO1CA78734 and PO1CA80139 as well as Philips Research.

References