Assessing the future of diffuse optical imaging technologies for breast cancer management

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Diffuse optical imaging (DOI) is a noninvasive optical technique that employs near-infrared (NIR) light to quantitatively characterize the optical properties of thick tissues. Although NIR methods were first applied to breast transillumination (also called diaphanography) nearly 80 years ago, quantitative DOI methods employing time- or frequency-domain photon migration technologies have only recently been used for breast imaging (i.e., since the mid-1990s). In this review, the state of the art in DOI for breast cancer is outlined and a multi-institutional Network for Translational Research in Optical Imaging (NTROI) is described, which has been formed by the National Cancer Institute to advance diffuse optical spectroscopy and imaging (DOSI) for the purpose of improving breast cancer detection and clinical management. DOSI employs broadband technology both in near-infrared spectral and temporal signal domains in order to separate absorption from scattering and quantify uptake of multiple molecular probes based on absorption or fluorescence contrast. Additional dimensionality in the data is provided by integrating and co-registering the functional information of DOSI with x-ray mammography and magnetic resonance imaging (MRI), which provide structural information or vascular flow information, respectively. Factors affecting DOSI performance, such as intrinsic and extrinsic contrast mechanisms, quantitation of biochemical components, image formation/visualization, and multimodality co-registration are under investigation in the ongoing research NTROI sites. One of the goals is to develop standardized DOSI platforms that can be used as stand-alone devices or in conjunction with MRI, mammography, or ultrasound. This broad-based, multidisciplinary effort is expected to provide new insight regarding the origins of breast disease and practical approaches for addressing several key challenges in breast cancer, including: Detecting disease in mammographically dense tissue, distinguishing between malignant and benign lesions, and understanding the impact of neoadjuvant chemotherapies. [DOI: 10.1118/1.2919078]

I. INTRODUCTION

The field of optical imaging in medicine has seen continuous growth for decades, and there is a wide array of technologies and applications in development and clinical use. The range of different optical hardware choices available leads to a complicated process of convergence upon the optimal system for each specific clinical need. For example, even within the categories of light sources, detectors, and light delivery, there are many dozens of options to choose from, and the choices made can drastically alter the data that is possible to be obtained. Two central benefits from optical imaging are the ability to gain molecular-level information and submicro-

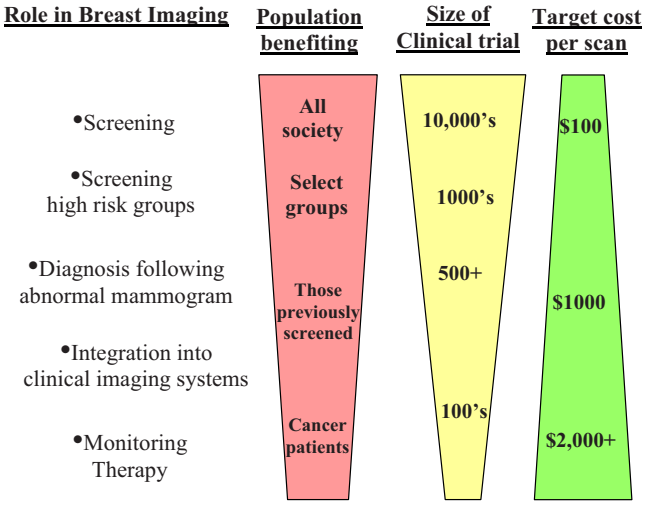

FIG. 1. A schematic illustration of the issues involved in determining a new technologies role in breast imaging is shown, with the main factors being the type of application (left column) and which population this then impacts, which will then determine the size of the clinical trial required to prove the technology is effective. Then ultimately there is a target cost per scan which will need to be considered for the technology to be economically feasibly in the current healthcare market.

scopic structural information, about the tissue function. Fundamental studies indicate that the molecular and cellular specificity are possible, in both endogenous tissue markers and with exogenous contrast agents. However, rapid medical translation can be slowed by the lack of convergence to a single technology, and yet strategic industry and academic collaborations can be used to help advance translation. The National Cancer Institute (NCI) has funded specific Networks for Translational Research in Optical Imaging (NTROI) through a competitive review process, whose mission has been to define technologies which have the highest potential promise for impact in cancer, and find ways to test and validate them in multicenter trials. The Network preparing this report was funded to advance optical imaging technologies that have high potential to translate into successful multicenter trials in a setting related to breast cancer management. The focus of this paper is to outline these promising technological innovations and look towards what development time scales they should be expected on.

In any imaging technology development, there is a key set of trade-offs which are dictated largely by the application needs. In Fig. 1, an illustration of the key needs in breast cancer detection, diagnosis, and management are listed on the left, along with estimates of the subject population who would benefit from the system, and an order of magnitude estimate of the scope of a clinical trial which would be needed to demonstrate the system utility. Additionally, the application area of the system will ultimately have a cost which makes the system financially viable for the application. For example, population wide screening programs would have widespread societal impact, yet would require clinical trials with potentially tens of thousands of people to prove the system efficacy, and ultimately could only be cost effective if the cost per person was as low as mammography, in the range of 100's of dollars per exam. In contrast, if an optical technology is used as part of a magnetic resonance imaging (MRI) scanner, then the population imaged would be considerably smaller, but the efficacy could be demonstrated with only hundreds of patients, and ultimately the cost per scan could be similar to MRI, which is in the range of a few thousand dollars per exam. While Fig. 1 is just a rough illustration, it is a useful guide to think about how the area of application helps determine the clinical trial needed to prove utility, and ultimately the cost effectiveness targets for the commercial scale system.

In the following sections the key opportunities for having an impact upon breast cancer management are outlined. The structure of the following sections is that each of the most compelling applications are outlined, together with a discussion of the most useful technologies using Spectroscopy, Imaging and Tomography. In some cases, single institutional trials are sufficient to study the problem and advance the technology, and in some cases multicenter trials are required to achieve a meaningful impact. This is in the context of both the trials ongoing presently, and those which will likely be carried out in the next decade. One goal of this work is also to help define areas where government and industry collaboration might be partnered, to advance the field of optical imaging in order to have useful impact in breast cancer.

II. MONITORING OF NEOADJUVANT CHEMOTHERAPY RESPONSE

One of the most compelling applications to be studied in the past few years has been the ability to track neoadjuvant chemotherapy response in breast cancer tumors. The ability to take measurements of light transmission through bulk tissue and recover absorption and scattering values, at multiple wavelengths, has provided the critical ability to quantify tissue chromophore concentrations *in vivo*. Convergence on one technology in this area is critical, since the numbers of subjects who would be imaged is relatively small and so unifying the technical implementation is critical to achieve meaningful summary data which can demonstrate efficacy. The cost of the instrument, the system accuracy, and impact upon patient management are all key factors, and choosing an application where no good tools exist today is also critical. As can be seen in Fig. 1, the population benefiting from this system would be those with locally advanced breast cancer, and because the need is acute, the ability to complete a clinical trial demonstrating efficacy is a little easier than in screening applications. Interestingly also, since the application is not widespread but targeted to those who need the system to assess their treatment efficacy, the cost per scan ultimately could be substantially higher, as treatments can typically be in the thousands to tens of thousands if they are truly effective. The NCI sponsored NTROI has been advancing the development of Diffuse Optical Spectroscopy to be used to track response to neoadjuvant chemotherapy in locally advanced breast cancer cases.

Neoadjuvant chemotherapy treatment is in widespread use, and is growing in its use in treatment of other types of

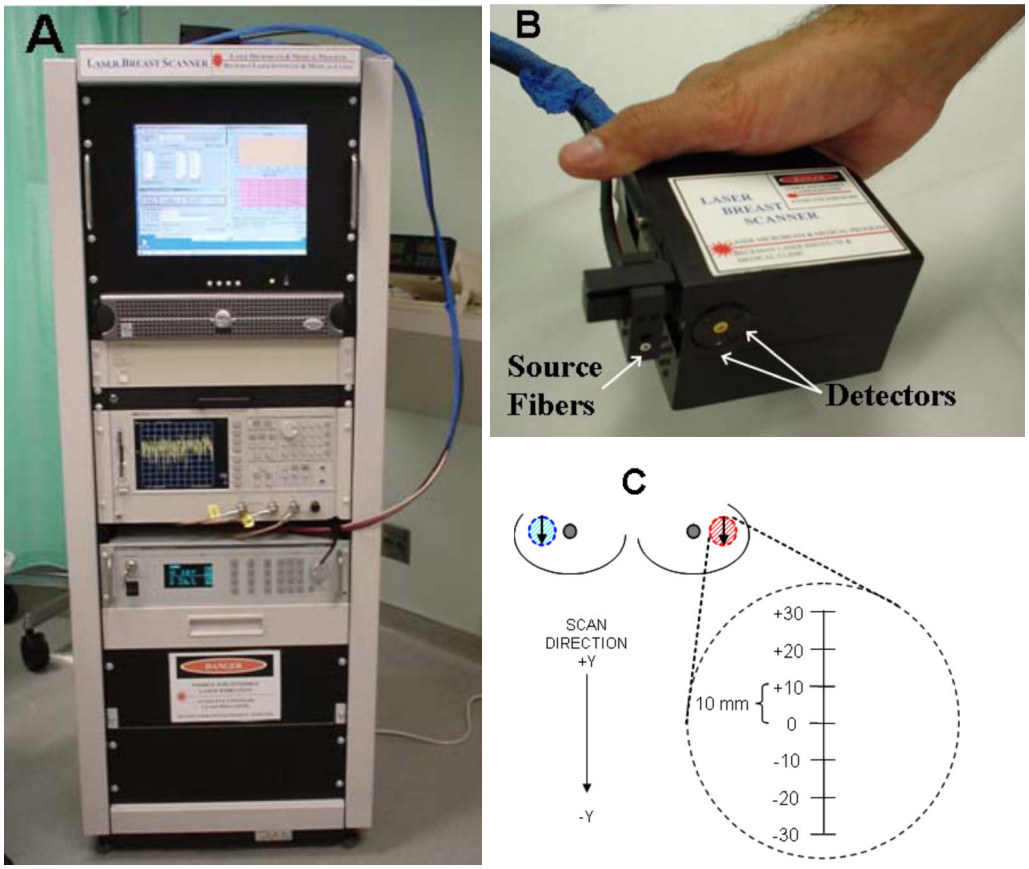

FIG. 2. The Laser Breast Scanner (LBS) system developed at the University of California Irvine, Beckman Laser Institute, which has been produced for multicenter trials of monitoring neoadjuvant chemotherapy response in breast cancer. The system electronics and console are shown in (A), and the tissue probe with light source fibers and light detectors in (B), and the procedure to take measurements across the tumor region (right breast) and the controlateral breast (left breast) are shown, with the probe being moved in 1 cm increments, to allow measurement of the on-tumor and off-tumor values of the tissue optical index (TOI).

cancer beyond breast. One rationale for this therapy is to allow tumor reduction prior to lumpectomy surgery of the tumor mass, thereby allowing smaller surgeries with better normal tissue sparing. The other major rationale is to reduce the probability of distant metastases prior to mastectomy or lumpectomy. However, about 30% of women with locally advanced breast cancer will not respond at all to neoadjuvant therapy,[1,2] so it is critical to determine which subjects are responding and which are not. While most of the decisions in this treatment scheme are done at the end of the chemotherapy that was prescribed, it is possible that earlier detection of nonresponse would be beneficial so that alternative therapies could be attempted earlier in the disease management process. The concept of neoadjuvant chemotherapy and monitoring the response has also been proposed as the optimal way to "test" if the patient will respond to chemotherapy, and this testing is ideally done prior to surgery. The optical imaging system being proposed for multicenter studies should provide both molecular absorber information and ultrastructural information from scattering. Early pilot studies have indicated that changes in tumor absorption can be observed within the first days after treatment,[3–7] and that the specificity of these changes can be as high as 95%–100%. The clinical goal in using the system would be to accurately screen treated patients and determine those who were not responding, such that they could be shifted to another more promising therapeutic approach.

A multicenter trial is under way with the system constructed at the University of California Irvine's Beckman Laser Institute, called the Laser Breast Scanner (LBS) (Fig. 2).[8,9] The LBS is a bedside-capable system that combines frequency-domain measurements with steady-state broadband tissue spectroscopy to measure complete broadband quantitative near-infrared (NIR) absorption and reduced scattering spectra of breast tissue *in vivo*. This technology solution is ideal for the task of scanning women for determining response to neoadjuvant chemotherapy for several reasons. The key factors involved in this decision are:

- Low patient numbers per medical center, requiring multicenter trial collaboration
- Requirement of low cost for initial multicenter clinical trials.
- Requirement of established system hardware and standard operating procedures for multicenter trials.
- Most tumors undergoing neoadjuvant therapy are large, and often near the breast surface, making the surface scanning approach a good option.

- Mulitiple track measurements over the tumor will avoid the confusion associated with interpreting imaging data in multicenter setting.

The LBS instrumentation and theory have been described in several previous publications.[10] The approach is highly stabilized and rich in information because of using multiple fiber-coupled laser diodes that are intensity modulated, with solid state detection. The diffusely transmitted spectra measured from the tissue are fit to a model of diffuse light transport, and are used to recover average tissue concentrations of oxygenated hemoglobin (ctO_2Hb), deoxygenated hemoglobin (ctHHb), total hemoglobin concentration ($ctTHb = ctO_2Hb + ctHHb$) tissue hemoglobin oxygenation saturation ($stO_2 = ctO_2Hb/ctTHb \times 100\%$) water ($ctH_2O$), and lipid concentration. A contrast function is used to combine DOS measurements to locate the location of maximum lesion optical contrast: Tissue Optical Index, $TOI = ctHHb \times ctH_2O/(\%\ \text{lipid})$. The parameters of this contrast function were determined from an evaluation of diffuse optical spectroscopy (DOS) measurements in a larger population of 58 malignant breast lesions. Tissue scattering is reported by the results of a power law fit of the form transport scattering coefficient $= A\lambda^{-SP}$, where λ is the optical wavelength. The probe is moved along a linear position on the surface of the tissue [Fig. 2(C)], and future versions of the system use will focus on 2D scanning in both x and y directions along the breast surface to map the tumor from above. The measurements must be made by placing the probe on the breast with light pressure to ensure contact. For comparison, a surface 2D scan is also performed at an identical location on the contralateral breast.

The goals for the multicenter studies ongoing with this system are:

- To assess therapeutic efficacy early in treatment with the LBS to allow future studies of tailoring treatment regimens for maximizing response, minimizing toxicity, and increasing overall survival;
- To provide quantitative, noninvasive monitoring of tumor physiology and treatment response, correlated with histopathology and MRI, will provide new insights regarding mechanisms of chemotherapy;
- To examine how dissemination of the LBS technology into general practice works, and increase the availability of potentially valuable technologies to a broader population.

III. SCREENING FOR SUBPOPULATIONS OF WOMEN

Screening women for cancer has become one of the largest success stories in preventative medicine, with annual mammography being the "standard of care" for women over the age of 50 in most of the developed world. But still there are populations where this screening program does not work well, and this is in women with:

- Highly radio-dense breast tissue.
- Known higher risk due to genetic factors.
- Complex breast tissue due to previous surgery.
- Younger women who are within the age range where annual screening is recommended.

In each of these groups, there are research studies ongoing to determine the best way to manage or indicate regular screening for cancer, yet the ideal situation of nonionizing radiation or more sensitive tools is attractive for these applications. The problems with screening in these groups largely fall into the logistics of:

- Contrast to noise problems with detecting abnormalities through dense or complex tissues
- Difficulty in imaging or scanning the entire breast volume
- Difficulty in justifying the cost of screening programs, prior to knowing the sensitivity and specificity of the system proposed.

This latter issue is really a key factor, since in many cases the first two problems may be fixed for given systems. The major factor is that once a system is chosen, there needs to be a large clinical trial done to assess the sensitivity and specificity of detection of tumors in each subpopulation (as indicated in Fig. 1), and these values can then help determine if the system is going to have clinical utility. There are major biological and clinical factors that influence the imaging, and so pilot trials have already been completed to assess the factors associated with age, body mass index, breast density, menstrual cycle effects, menopausal status, and hormone replacement therapy status.[9,11–13] Now that these are reasonably well understood, it is possible to design screening studies which will have matched controls to assess the system performance in the relevant subpopulation. As indicated in Fig. 1, screening has maximal benefit, but because the application is applied widespread the cost to society is enormous, and drives down the target cost per scan to very low values. The optimal societal benefit in screening is likely in those not well served by existing mammography programs, such as young women and radio-dense women. As the numbers of subjects in these groups is still very large, the medical impact of a successful technology would be enormous, albeit potentially costly.

For the problem of screening these specific subpopulations of women, there are two technological approaches which will work. The LBS mentioned in the previous section is a logical choice to screen women with a lower cost solution. This system would require scanning the entire breast surface and is maximally sensitive to the outer few centimeters of tissue under the probe. Alternatively, a breast spectral tomography system could be used for transmission tomography imaging of the breast. A couple of such systems have been developed to an advanced clinical trial stage [Fig. 3(A)] with approval for sale in several countries, and several laboratory research systems have been developed and used in large clinical trials [Figs. 3(B) and 3(C)]. The advantage of these systems is that the tumor characteristics can be imaged while the patient is lying in a prone position, and there is reasonably good coverage of most of the breast. There are still problems with imaging very small or very large breasts, as there are in mammography, yet for a majority of women,

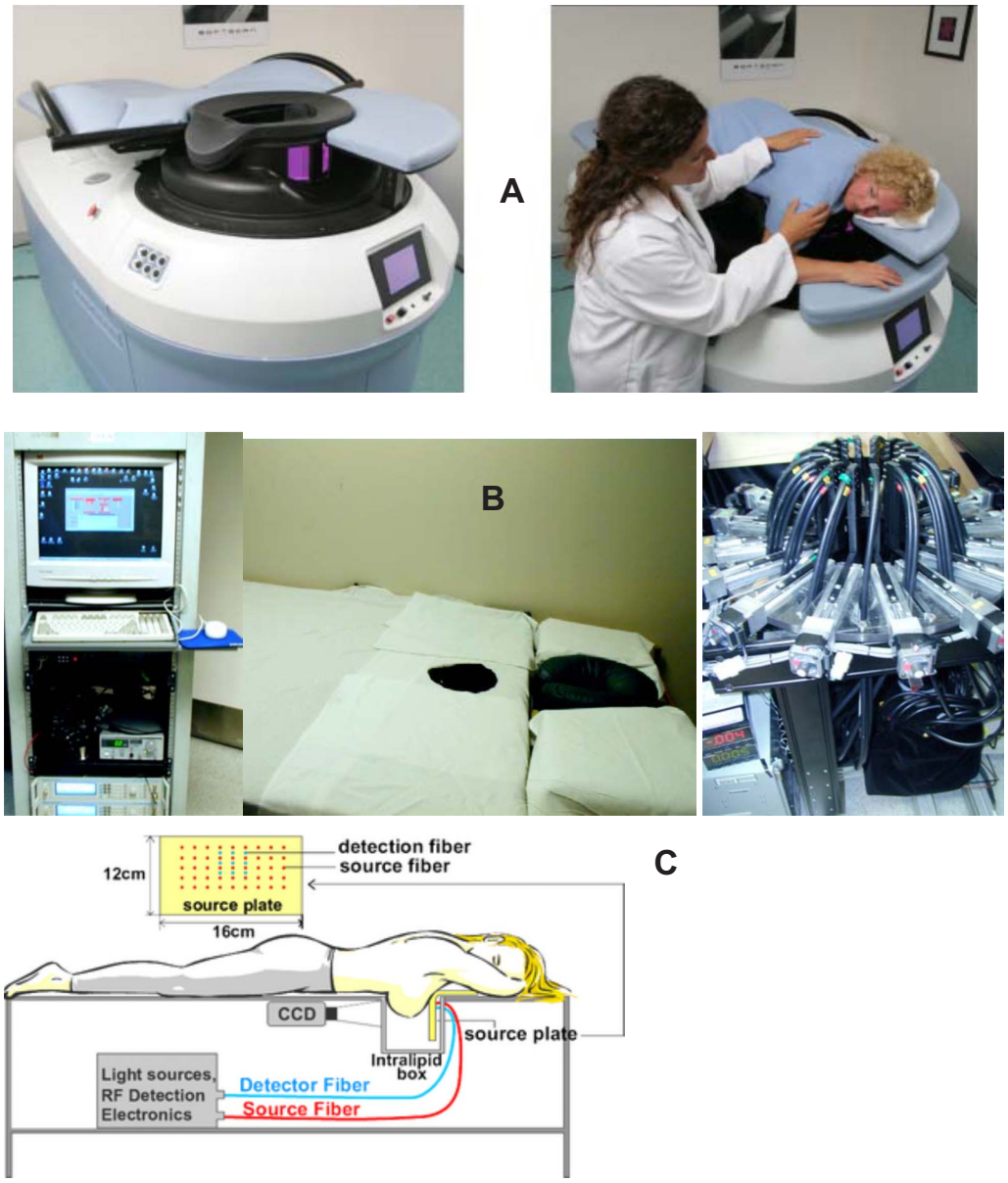

FIG. 3. Tomographic imaging systems developed for breast tumor characterization and imaging during therapy have been developed and large clinical trial results have been published. The commercial system from ART Inc. (see Ref. 15) is shown in a photograph (A), and research at Dartmouth resulted in the system shown in (B) (Refs. 14, 28, and 29), and a schematic of the system at the University of Pennsylvania is shown in (C) (Refs. 6 and 30). Each system uses multiple sets of measurements at multiple wavelengths of NIR light, transmitted through the breast to reconstruct images of hemoglobin, oxygen saturation, water, and scattering values.

this imaging can be done readily with a visit taking less than 30 min. The utility of these systems in a truly widespread screening application is still unproven, but clinical trials are ongoing to assess sensitivity and specificity in subgroups.

IV. OPTICAL AS AN ADJUNCT IMAGING TOOL

Optical imaging as an adjunct device to mammography or ultrasound imaging is a natural choice, because the information gained with the optical signal is distinctly different from that of the clinical imaging information. Near-infrared scanning of suspected abnormalities could provide the added information required to better determine the malignancy status, and either help determine whether biopsy is needed, or ultimately track suspected abnormalities over time to detect malignant types of changes. There have been several commercial ventures aimed at this particular technology space in the health care market, and two devices have gained approvals in some countries and in an evaluation phase in the U.S., including ComfortScan (ART Inc., Montreal Canada) and Computed Tomography Laser Mammography system (CTLM) (Imaging Diagnostic Systems, Inc., Plantation FL). Research in this area has also been carried out by a European consortium and by Philips Medical Systems. The key to success in this area has been to find an optimal way to maximize the clinical use of information of the optical image alongside

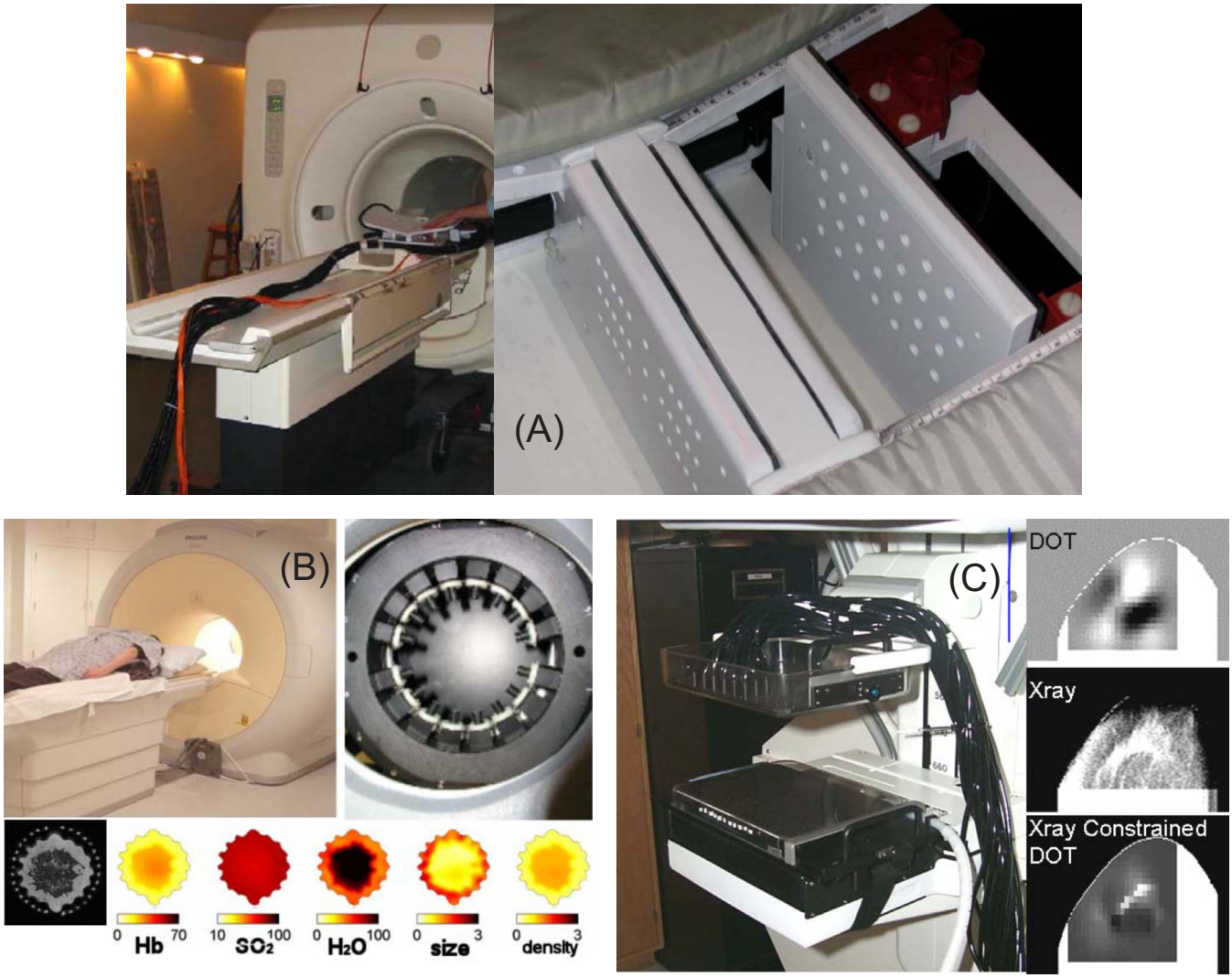

FIG. 4. Hybrid Modality systems have been developed and used in pilot clinical trials to characterize tumors and test the synergy in having mutual information and the ability to combine information data sets to create a new class of hybrid images. The University of Pennsylvania system was the first such device (A) (Refs. 26 and 27), and similar systems were built into a 3Tesla MRI at Dartmouth (B) (Refs. 18 and 20), and into an x-ray tomosynthesis system at the Massachusetts General Hospital (C) (Ref. 31).

standard mammography. This is more of a clinical workflow question and significant focus has been on making a workstation model which could be truly integrated into a radiology department. So interestingly in this application, the actual success may depend more upon the business model, and the ability to integrate the information into a standard Radiology workflow, rather than the system, yet system performance must also be at a high level.

Academic research studies have examined the combination of optical tomography as an adjunct to mammography, and publications by Poplack *et al.*, report on the first blinded, age-matched control trial using NIR spectral tomography as additional information to mammography, and the data indicate that for tumors with sufficiently high hemoglobin signatures, that there is definitely added information from the NIR images.[14] The analysis of data from the ART system indicates that when the mammography and NIR images are used side by side with co-localized analysis, that the ROC values can be in the range which should be highly useful clinically.[15] The clinical trials to assess these systems in larger cohorts are still ongoing, and useful conclusions should be reached within a few years about the feasibility of using NIR as an adjunct to mammography.

V. OPTICAL SPECTROSCOPY INTEGRATED INTO CLINICAL IMAGING TOOLS

One key way for optical imaging to readily be integrated into medicine is as an "add-on" to larger and currently accepted clinical imaging systems, such as mammography, ultrasound (US), x-ray computed tomography or tomosynthesis, and Magnetic Resonance Imaging (MRI). Research in system integration has taken place in all of these areas, with a primary focus on breast imaging, to follow up on some earlier screening. Illustrative systems are shown in Fig. 4, with the first MR coupled system shown (A), and a Philips/

NIH sponsored 3T MR-coupled system being tested currently (B), and the NIR system built into an x-ray breast tomosynthesis system (C). While the primary screening modality for the breast is x-ray mammography, there has been comparatively little study of how to introduce optics into this modality, indicating that integration with the other modalities would lead to applications which are not in the screening area. Thus the potential for adding optics into a secondary imaging modality then lies in the area of providing information which can differentiate the diagnosis of the lesion, or perhaps track therapy response.

If the key role for optics integrated into clinical systems is to provide functional information for a targeted region within the breast, then the system integration needs to be carried out to maximally utilize the information from the two systems in a complementary or ideally synergistic manner. A key method of integration is then to maximize the spectral content of the optical hardware and utilize the spatial prior relations from the clinical imaging system.[16–20] This approach to integrating spectral constraints and spatial prior information as a constraint has been demonstrated in tumor imaging,[20] and can now be implemented with optimized software algorithms becoming available through the network. As illustrated in Fig. 1, DOS imaging within other imaging devices would have a cost that was likely matched to the system it was coupled to, such that DOS coupled to ultrasound would likely have to be quite inexpensive to make an impact, whereas DOS coupled MR could be considerably more expensive since the latter cost is limited by the MR mainly. The economic feasibility of these hybrid systems is a little uncertain at present, however performance will likely have a major influence on the cost which is appropriate.

Optical tomography has been integrated into a breast x-ray tomosynthesis system [Fig. 4(C)] at the Massachusetts General Hospital, and is undergoing clinical trials.[21,22] Because of the widespread use of x-ray imaging of the breast, this combination makes fundamental sense, and may provide additional information where mammography has limited efficacy, such as in the dense breast or for distributed or complex lesions.

Additionally, soft tissue imaging with US is the natural follow on procedure for certain diagnoses, and integration of optical spectroscopy into this has been productive and led the way towards region-based estimation of tissue properties.[23–25] This approach makes sense for US, as the region to be characterized is usually known when US is being used, and the goal is then to provide as much information about the tumor as is feasible. The ability to image hemoglobin, oxygen saturation, and scatter has all been shown, with strong potential for added diagnostic information.

The integration of diffuse tomography into MRI was a key development which was initially pioneered at the University of Pennsylvania[26,27] and this work is being carried on to explore ways to synergize the mutual information through the use of MR-derived spatial constraints in the diffuse optical imaging (DOI) spectroscopy,[18,20] and the exponential growth of breast MRI in recent years makes these developments of heightened importance [Figs. 4(A) and 4(B)]. With MR, there is increased ability to constrain the optical property recovery both spatially as well as in chromophore concentrations, as the MR can yield water and fat maps which can be used to constrain the spectral recovery of hemoglobin, oxygen saturation, scatter, and exogenous agents.

The integration of NIR into clinical imaging is a natural step in the progression of integration of clinical information into a streamlined series of information sources. One illustration of this with widespread acceptance is the newly used hybrid PET/CT scanners, where the PET information has gained much wider appreciation through the ability to superimpose the scan on the high resolution CT image, and further to allow enhancement of the image quality through postprocessing based upon the CT. Similar to this, overlay of NIR spectral data on the MR scans and enhancement of the NIR spectral data quantitatively should allow easier clinical acceptance of this new information stream.

VI. CONCLUSIONS

The four applications listed here are key areas where the healthcare need overlaps very well with the emerging technology which is available in the next decade. Each area requires refinement of the NIR technology or completion of multicenter clinical trials to verify that the technology will truly be a useful solution to the problem. NIR spectral tomography of tissue has had a rich history of development in NIH funded work, and some of the designs discussed in this overview are a result of decades of development. Advanced stage clinical designs that will be advanced towards multicenter trials are desperately needed to carry out these validation trials. Coordination of these trials with the established medical clinical trials bodies such as the National Cancer Institutes Imaging Clinical Trials program or through the American College of Radiology Imaging Network (ACRIN) would be the ideal way to ensure that these technologies are advanced appropriately with maximal overlap with other information sources.

In some cases the business model involved in the system development can lead to success or failure of the technology, however designs which have been vetted through both peer-reviewed development as well as business plan evaluation would be ideal to ensure that the right technology is advanced with the greatest promise for success. Ensuring that academic-industry partnerships have a pathway for this cooperation is critical, in a manner which is not too encumbered by limited funding issues, but also provides room for competition and intellectual property preservation. This is a complex landscape in which to develop advanced technologies, but the National Cancer Institute has made the first solid step in this process through sponsorship of the Network for Translational Research in Optical Imaging. Development of optical contrast agents which will provide true molecular or compartmental specificity for cancer still remain to be developed to the point of FDA approval and commercial distribution, however large amounts of research are still under way in this area. It is likely that these exogenous contrast agents will be used in breast cancer imaging or therapy, but

the timeline for FDA approval for human use is still quite uncertain at this time. The technologies outlined here for intrinsic contrast imaging are capable and ready to be used in molecular contrast imaging as well, so it is likely that after the first round of multicenter trials begin in endogenous imaging, that this may facilitate the means for studying contrast agents in a multicenter setting as well.

This paper is a summary report from one of these sponsored networks for translational research in optical imaging, where the outcome of the network has been exactly focused on providing a convergence in the space of advanced NIR technology, breast cancer health care need, and business development capacity. The clinical trials proposed here will be carried out over the next decade or so, and will likely have a direct impact on both the technologies, businesses, and medical practice involved in breast cancer detection and management.

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