Sono-Contrast Spectroscopy for Cancer Virtual Biopsy in LMIC Settings

Yan Yu
Department of Radiation Oncology
Thomas Jefferson University
Philadelphia, U.S.A.
Yan.Yu@Jefferson.edu

Lydia Liao
Department of Radiology
MD Anderson Cancer Center at Cooper University Hospital
Camden, NJ, U.S.A.
Liao-Lydia@Cooperhealth.edu

***Abstract*—We present an initiative to adapt, optimize and productize a multimodal breast cancer detection technology, termed "S*ono-Contrast Spectroscopy*" (SCS), for use in Low- and Middle-Income Countries (LMIC) to facilitate point-of-care early detection of breast cancer. The prototype SCS scanner was developed from proof-of-concept in vivo preclinical research and subsequently through a first-in-human pilot clinical study. Quantitative evaluation with histopathology data from tissue biopsy of the interrogated lesions as ground truth demonstrated that the SCS technique achieved very high discriminating power as measured by sensitivity, specificity and Receiver Operating Characteristics (ROC) analysis; the Area Under the Curve (AUC) ranged from 0.90 to 0.95 in racial/ethnic subgroup analysis, and was equal to 0.91 over the entire study group of 66 subjects. Particularly of relevance to global health applications in the LMIC settings, the SCS technique does not require clinical subspecialty interpretation, is easy to deploy and operate, has no disposable or consumable parts, reports diagnostic results instantaneously, and potentially offers an effective alternative to expensive and invasive large-core vacuum-assisted needle biopsy followed by subspecialty pathology evaluation, all of which may be inaccessible in LMICs. Significant steps towards global health deployment in these settings are outlined.**

Keywords-cancer diagnosis; spectroscopy; biopsy; near infrared; focused ultrasound.

I. INTRODUCTION

According to the World Health Organization, breast cancer is the top cancer in women in the developing world, and its incidence is increasing due to increases in life expectancy and urbanization; furthermore, the majority of breast cancers that develop in Low- and Middle-Income Countries (LMICs) are diagnosed in very late stages [1]. Therefore, early detection in order to improve breast cancer outcome and survival remains the cornerstone of breast cancer control. Population-based cancer screening is a highly complex public health undertaking. Mammography screening is very costly and is cost-effective and feasible only in countries with good health infrastructure that can afford a long-term organized population-based screening program. Breast cancer survival rates vary greatly worldwide, ranging from 80% or over in North America, Sweden and Japan to around 60% in middle-income countries and below 40% in low-income countries [2]. The low survival rates in less developed countries can be explained mainly by the lack of early detection programs, resulting in a high proportion of women presenting with late-stage disease, as well as by the lack of adequate diagnosis and treatment facilities [1].

Early detection of breast cancer has been proven to reduce mortality by about 20% to 35% [3]. Histopathological examination is considered to be the "Gold Standard" for definitive diagnosis of cancer but requires adequate tissue samples that are collected through biopsy procedures capable of sufficient tissue retrieval. Of the two major approaches for breast biopsy, needle biopsy and open excisional biopsy, needle biopsy is the most commonly practiced standard in affluent countries because it is less traumatic, produces little or no scar, allows quicker recovery, and is less expensive.

Relative to LMIC resources, however, these techniques can be prohibitively expensive (e.g., *disposable* large-core needle), requires tissue transfer to pathology facilities and expert review (not always available or timely), and results in patient call-back (often impractical in remote/rural settings). Open excisional biopsy suffers from these same drawbacks, and results in greater trauma and postsurgical care. At the same time, it is well known that current methods for breast cancer surveillance including breast self-exam (BSE), clinical exam, mammography, ultrasound and even Dynamic Contrast-Enhanced (DCE) MRI lead to high proportions of unnecessary biopsies (on average, only 1 in 3 to 4 biopsies results in a cancer diagnosis even in highly subspecialized breast care centers). In less affluent healthcare environments, some or many of these proven diagnostic modalities may be unavailable or not uniformly affordable by all patients. Clearly, there is a severe unmet need in LMICs for realizing adequate and accessible diagnosis of treatable early stage breast cancer.

We have successfully developed and validated a breast cancer diagnosis tool using combined Near Infra-Red (NIR) Diffuse Reflectance Spectroscopy (DRS) and Low-Intensity Focused Ultrasound (LIFU) modulation of blood flow in vivo. We have shown, first in preclinical animal models and recently in a pilot clinical study, that focused ultrasonic pulses create different blood flow and tissue oxygenation signatures depending on whether the tissue being interrogated is malignant or normal; these differences can be markedly discriminated via NIR spectroscopy, with pronounced contrast in spectral parameters. Thus we termed the technique sono-contrast spectroscopy (SCS). Importantly, this technique overcomes a prevailing problem

 ISBN: 978-1-61208-359-9

in using noninvasive optical tissue interrogation methods, i.e., the spatial or targeting certainty becomes highly degraded due to NIR light propagation in tissue. Numerous physical, mathematical or multimodal hardware devices have been applied to solve this fundamental "ill-posed" problem in biomedical photonics. Here we deploy the fundamental solution that the acoustic sonication is focused on the target lesion unequivocally; any change in spectrophotometric values before, during and after sonication is characteristic of the lesion being interrogated. Thus there is no need for multiple expensive source/detector arrays, inverse solutions, a priori multimodal information or multimodality encoding, leading to a simple, low-cost and somewhat elegant device.

Importantly, the SCS in vivo scans are completely noninvasive: both the ultrasonic and NIR light intensities needed are well below U.S. Food and Drug Administration (FDA) recommended safety levels. Additionally, computer-aided discrimination of cancerous vs. normal findings can be made instantly, following a 2-min. or less sonication and light illumination/spectral acquisition time. If proven sufficiently accurate for breast cancer diagnosis, the proposed technique can be considered "*virtual biopsy*" with real-time reporting of study results offering rapid turnaround in busy LMIC breast clinics.

There is no disposable component in the SCS exam; only routine cleaning/disinfecting is needed after each patient's visit. In the long run, focused ultrasonic transducers (note: these are *not* sonographic probes), low-power NIR lasers and photodiodes can all be mass assembled from off-the-shelf components; RF signal generation can be achieved in software and dedicated amplification circuitry. Data transmission, analysis and diagnostic algorithm updates can make use of wireless technology (e.g., Bluetooth), consumer electronics (e.g., Smartphone apps) and cloud computing. Thus, it is entirely feasible that the fully productized device will be low-cost, battery-driven, and usable by non-specialists.

We envision that the eventual SCS device will be handheld, reports examination results instantly in two mode: (a) simple – such as green, yellow and red LEDs for benign, needing further interrogation and highly suspicious of malignancy; (b) comprehensive user-configurable interface where patient-specific factors such as age, racial/ethnic group, Body Mass Index (BMI), cup size, and other relevant health/lifestyle parameters can be associated with the diagnostic finding. The globally deployed SCS device will use cloud-computing and massively distributed learning paradigms to improve its diagnostic accuracy and adapt to new LMIC environments or racial/ethnic settings. The overall goal of this initiative is to push breast cancer diagnosis progressively earlier, so that low-cost treatment regimens such as surgery alone, or breast-conserving surgery plus simple whole breast tangential radiation, are still effective in eradicating the disease.

Even in LMIC communities where breast ultrasound and/or mammography is accessible to patients, there is still a large gap between a suspicious imaging finding and positive diagnosis by surgical excision. In affluent countries, this gap is being closed by improved accessibility of DCE MRI, Contrast-Enhanced Spectral Mammography (CESM), 3D/tomosynthesis, and ultimately large core needle biopsy with tissue histology diagnosis and biomarker profiling. Absent of such expensive technologies, patients in LMICs are faced with the choice of surgical excision with high probabilities of negative result, or delayed diagnosis of cancer. The proposed SCS technology can be used as a low-cost method to close this gap by identifying suspicious lesions that are associated with high likelihood of malignancy.

Accurate surgical excision also requires technology guidance. In affluent countries, this is achieved by wire localization under stereoscopic imaging, ultrasound and MRI, or radioactive seeds. In LMIC communities where facilities or patient logistic does not permit such complicated precision guidance, the SCS technology may become a useful tool for the surgeon to identify the tumor extent/location immediately prior to incision. The standard of care for breast cancer treatment in the U.S. and many developed countries is lumpectomy plus radiation (or mastectomy). When radiation therapy is inaccessible in LMICs, the standard care is relatively unclear; however, anecdotal evidence suggests that limited excision/lumpectomy alone sometimes represents the entire treatment. In such cases, arming the surgeon with a real-time cancer delineation tool like the SCS probe can potentially change the probability of local control vs. recurrence.

In affluent countries, modern standard of care consists of large-sample tissue histology diagnosis plus biomarker profiling. In LMICs, however, even the cost of large core sample retrieval can be prohibitive. The decision for open surgical excision biopsy is considerably more difficult because of its invasiveness. Through added diagnostic value in using the SCS technology, we hope to inform the patient more effectively before undergoing highly invasive and costly procedures that may be unnecessary, thus the concept of "virtual biopsy".

At the same time, the cancer screening initiative we plan to implement would serve as early sentinel events pointing to the need for comprehensive diagnostic workup in patients with highly suspicious breast lesions. In LMIC settings, low-cost surgical excision (mastectomy or wide-excision lumpectomy) may be an accessible option. Radiotherapy may or may not be accessible; chemotherapy or targeted biologics may be out of reach. Early diagnosis of localized, non-metastatic breast cancer could be an important demarcation between curative vs. palliative treatment plans.

In short, in the SCS technology we hope to achieve the complementary goals of eliminating unneeded invasive interventions and discovering breast cancer before it becomes expensive or impractical to treat.

II. SONO-CONTRAST SPECTROSCOPY PRECLINICAL STUDIES

In 1971, Dyson *et al*. reported that stationary ultrasound waves caused stasis of red blood cells *in vivo* [4]. In 2006, we reported our initial animal study, supported by NCI R21 CA107860, in which this effect was first used to differentiate

 ISBN: 978-1-61208-359-9

tumor from normal leg muscle tissue in mice [5]. Under normal physiological conditions, oxygen dissociates from hemoglobin molecules in red blood cells to replenish the oxygen supply in tissues as blood flows through the vessels. When standing wave ultrasound is used to slow or stop the blood flow, the ratio of oxy- vs. deoxy-hemoglobin content decreases, which can be measured using NIR spectroscopy. We hypothesized that the effect of this acoustic radiation force on blood flow and stasis would be different in normal vessel network morphology vs. malignant, angiogenic morphology (lack of directionality, chaotic network, leaky vessel walls, etc.). The "*sono-contrast*", i.e., changes in spectroscopic parameters due to administration of ultrasound acoustic force, was indeed found to be strong in normal vasculature and absent in tumors, thus serving as an excellent discriminator of benign vs. malignant vascular morphology in the *in vivo* model [6].

TABLE I. PANEL OF SPECTROSCOPIC PARAMETERS WITH STATISTICALLY SIGNIFICANT CORRELATION WITH IMMUNOHISTOCHEMICAL PARAMETERS

Dependent Variable	Statistically Significant ($p < 0.05$) Predictors from Regression Analysis	*p value*
Percentage of perfused vessel area in analysis area	Maximum minus minimum of the ratio signal with baseline trend subtracted	*0.031*
	Standard deviation of the ratio signal with baseline trend subtracted	*0.015*
Average distance between all vessels in analysis area	Maximum minus minimum of the ratio signal with baseline trend subtracted	*0.008*
	Standard deviation of the ratio signal with baseline trend subtracted	*0.005*
Mean EF5 intensity for all vessels	Difference between the endpoint values of the baseline trend line	*0.013*
Mean EF5 intensity for perfused vessels	Difference between the endpoint values of the baseline trend line	*0.012*
Standard deviation of average distance for all vessels	Maximum minus minimum of the ratio signal with baseline trend subtracted	*0.023*
	Standard deviation of the ratio signal with baseline trend subtracted	*0.014*

To study the physiological differences between normal vasculature and tumor vasculature, immunohistochemical studies were then conducted on the mouse muscle tissue and tumor samples following imaging and cryostat sectioning. Results of regression analyses showed that certain spectroscopy signals are significantly ($p = 0.005$ to 0.013) correlated with immunohistochemistry analysis of a panel of variables including percent area of perfused vessels, total number of vessels, mean distance between vessels (both total and perfused), and EF5 intensity (see Table 1) [5]. These findings further support the hypothesis that SCS is a functional reporter of vascular microenvironmental variability, and strongly suggest that SCS may be used to characterize tumor neoangiogenesis, proliferation and aggressiveness.

III. SONO-CONTRAST SPECTROSCOPY PILOT CLINICAL STUDY

A. *Instrument Design*

Based on the encouraging animal study results, we designed a human breast SCS scanner [7][8] and conducted a pilot clinical study to evaluate the diagnostic accuracy of this multimodal detection method. The scanhead was designed to deliver focused acoustic radiation fields up to about 2.4 cm deep in tissue. Two 1 MHz focused transducers (Channel Industries, Santa Barbara, CA) were aligned orthogonally inside the scanhead to create a focal area at the intersection of the axes. A commercial ultrasound probe (Philips L12-5, Valhalla, NY), located in the same plane as the focused transducers, was used for image co-registration with the NIR spectroscopy information, tissue density information and blood flow information. The ultrasound probe and focused transducers have two degrees-of-freedom, so that the focal zone can be scanned in tissue depth-wise and laterally. Three force sensors (Honeywell model 53, Morristown, NJ) were incorporated on the lower concave compression plate of the scanhead to measure the force exerted on the breast.

The optical spectroscopy system consisted of 18 customized 15-foot long and 2.5-mm diameter fiber bundles terminating at the concave bottom plate of the scanhead. Out of these 18 fiber bundles, 6 were used as sources and 12 were used as detectors. The 6 sources were illuminated by two laser diodes (LG-Laser Technologies, Germany) through a multichannel optical switch (O/E land Inc., Canada) that had 2 input channels and 6 output channels. Diffuse reflectance signals were collected by the 12 detectors, amplified by 12 avalanche photodiodes (APD) (Hamamatsu C5460-01, Bridgewater, NJ), and then transmitted through 1 multi-channel data acquisition card (National Instrument, Austin, TX) to the computer for analysis.

The ultrasound imaging probe was connected to a commercial ultrasound system (Philips iU22, Valhalla, NY) for image co-registration. The focused ultrasound transducers were driven by a function generator (Agilent 33250A, Santa Clara CA) connected to an RF amplifier (Amplifier Research 25A250A, Souderton, PA). During the operation, the forward and reverse power level was monitored via a directional coupler (Amplifier Research DC3010, Souderton, PA) using an oscilloscope (Tektronix TDS 2022, Richardson, TX), for ensuring electrical safety. A mobile hydraulic cart was used to host the instruments.

 ISBN: 978-1-61208-359-9

According to ANSI Z136.1 (1993) Safe Use of Lasers, for wavelength 0.647-0.905μm, the maximum permissible exposure (MPE) to skin is 0.2-0.5 $W \cdot cm^{-2}$. We selected 0.2 $W \cdot cm^{-2}$ as the threshold. Two Continuous Wave (CW) laser diodes were used in the spectroscopy system: one had a wavelength of 685 nm with the maximum output of 50 mW; the other had a wavelength of 830 nm with the maximum output of 110 mW. The power output for the two laser systems can be adjusted using the knob in the front panel. The threshold laser output at the source terminals was calculated to be 9.8 mW for the two laser units. A laser power meter system (Coherent LabMax, Santa Clara, CA) was used to calibrate and mark the corresponding threshold positions on the two units.

Based on the FDA guideline, the derated global maximum acoustic output of the diagnostic ultrasound equipment should not exceed Pre-amendments acoustic output exposure levels, i.e., derated Spatial Peak Temporal Average Intensity $I_{SPTA} \leq 0.72$ $W \cdot cm^{-2}$. We calibrated the acoustic radiation fields to ensure that it was within the limit. The acoustic focal spot having the maximum peak-positive voltage signal on the oscilloscope was found at about 2 cm below the bottom plate, which is the designed intersection of the axes of the two focused transducers. The I_{SPTA} was determined to be 0.4 $W \cdot cm^{-2}$, below the FDA ultrasound limits of 0.72 $W \cdot cm^{-2}$. The focal spot was then registered in the ultrasonography system for image guidance during the pilot clinical study. This calibration established the baseline of the dual-transducer focused acoustic radiation field. A Quality Assurance (QA) protocol was formulated based on the same procedure.

B. Clinical Study Results

Clinical study was carried out under an Institutional Review Board (IRB) approved protocol at Cooper University Hospital, NJ. The intended patient populations were those who present with a solitary mass in the breast that required ultrasound-guided tissue biopsy to rule out malignancies. The study was scheduled to be performed on the same day as biopsy. Once the patient signed the consent form for participation, the SCS scanning procedure would first be performed. After completing SCS scanning, the patient would be re-prepped using sterile technique for the standard needle biopsy procedure. Usually 3-4 core biopsy specimens were obtained for the same mass using large core biopsy needle. The approximate location of each core would be documented. Based on our clinical experience, the time taken from prep to first tissue removal was approximately 10 min. This time interval should be sufficient for the reversible process of vascular compression by LIFU to recover fully to the original state [4,9]. Tissue histology was obtained for all patients from the standard pathology reports. This information served as ground truth for developing the Computer-Aided Diagnosis (CAD) algorithm and validating its effectiveness.

The collected data stream consists of LIFU signals and NIR diffuse reflectance spectroscopy signals together with time stamp. They are first synchronized and segmented into 12 channels (corresponding to the 12 detectors). The diffuse reflectance spectroscopy signals are first processed using moving average technique to remove the noise and smooth the data. Discrete wavelet analysis is then used to further process the data, which involves using filters of different cutoff frequencies to analyze the signal at different scales.

A total of 66 patients were enrolled with informed consent under the IRB-approved protocol. Subsequent biopsy of each index lesion revealed 14 histologically-proven cancers (8 IDC, 4 ILC, 1 metastatic adenocarcinoma in lymph node, 1 invasive mammary carcinoma with ductal and lobular features; final staging 1A to 4). Using histology gold standard as ground truth, the predictive accuracy of SCS incorporating sophisticated wavelet analysis was evaluated [10]. Results of this human study corroborated the animal study. By exploiting the sono-contrast differences and imaging features, we have developed a panel of spectral and imaging biomarkers that demonstrates high discriminating power. It was found that this methodology predicted cancer vs. non-cancer with sensitivity of 93% at specificity of 81%; the area under the ROC curve ("area under the curve", or AUC), was determined to be 0.91 [11]. In comparison, reader-averaged AUC for mammography has been generally reported to be 0.70 [12]. Furthermore, additional subgroup analysis revealed that certain spectral and imaging biomarkers in the panel could discriminate between ductal and lobular cancer subgroups (p=0.022), and between HER2 negative 0 vs. 1+ subgroups (p=0.044) [11]. These subgroup analysis results further reveal that SCS may be used to interrogate and characterize breast cancers. This first-in-human trial clearly demonstrated the effectiveness of SCS as an *in vivo probe* of invasive breast cancers.

We also performed secondary analysis of the clinical study data by racial/ethnic groups including "White" (non-Hispanic), "Hispanic" and "African American" subgroups [13]. While the pilot study was not powered to generate definitive conclusions, it was found that subgroup-specific tuning of the diagnostic algorithms may lead to incremental improvements to diagnostic accuracy. For example, AUC was 0.95 for "White", 0.92 for "African American", and 0.90 for combined "African American"+"Hispanic" subgroups, respectively. Bootstrap resampling method was applied to overcome the data limitation; thus, these results should be regarded as suggestive of potentially even more improved efficacy in LMIC-specific racial/ethnic populations.

IV. SYSTEM ADAPTATION FOR LMICS

A. Low-power, Portable Configuration

The early generation instrument was tested with attenuated intensities in both the optical and the ultrasonic subsystems. The clinical data revealed that substantially low-powered optical and ultrasonic modules would be effective in eliciting contrast in blood flow/oxygenation between benign and malignant masses. Additionally, as few as one well-selected light detector channel (out of 6) was sufficient for diagnostic data collection. Thus, we have identified significant opportunities to eliminate over-designs to achieve a modular system with portable ultrasonic generator,

 ISBN: 978-1-61208-359-9

miniaturized transducers and off-the-shelf optical bench. Furthermore, the original design incorporated an imaging ultrasound probe in the scanhead for image guidance. Considering the likelihood that sonographic equipment may not be readily available in LMIC clinics as well as the viable alternatives found in the pilot clinical study (such as using a standalone imaging probe to mark the location and depth of interrogation), the imaging probe has been eliminated from the second-generation device design. Also eliminated are all scanning mechanisms in the lateral and depth directions; probes with sonication depths of 0–1, 1–2, 2–3, and 3–4 cm will be selectable, with appropriate standoff bolus as needed. Thus the new device design is predominantly "point-and-shoot" in operation. Together with near real-time CAD reporting of results, this design will offer a point-of-care virtual biopsy assay for cancer detection in low-resource healthcare environments.

B. Smart Diagnostics and Cloud-based QA Repository

Quality control of SCS clinical measurement data is critically important for diagnostic algorithm self adaptation and distributed learning (see Section C, below). The opportunity for non-expert or minimally trained healthcare providers to use a simple and noninvasive "point-and-shoot" device on patients further highlights the need for built-in QA surveillance. Excessive movement of the handheld probe during a point data acquisition period (which lasts for 105 sec. in our initial clinical study and is reducible to 36 or minimally 24 sec. in the second-generation) will cause signal breaks or noise in DRS, and may perturb LIFU sonication pulses. Such unwanted movement will be detected using built-in accelerometer chip with associated user warning/guidance and, if necessary, repeat data acquisition. Poor acoustic field contact can potentially lead to false positive findings; thus it is important to ensure consistent probe-tissue coupling. This will be monitored using built-in hydrophone circuit at the probe side. Similarly, NIR light-tissue coupling is essential for adequate illumination and DRS signal detection. Smart diagnostics on the collected spectral signal will be carried out in real-time to detect poor probe-tissue contact by analyzing the reflectance above ambient background signals, and communicated through simple user interface on the device.

In addition to the self-diagnostic functionalities built into the device to prevent erroneous use or data collection, anonymized study data from each examination can be transmitted to centralized QA repository using modern wireless technology. To achieve best interconnectivity for these purposes, integrate wireless capabilities (Bluetooth, WiFi) and Smartphone/tablet compatibility will be incorporated in the final product. Where the device is not used in online mode (e.g., in rural settings where WiFi or wireless connection is off), the data transmission will occur when the system is docked with online connection after field use or in charge mode. These data will include: sonication pulse heights and widths at both input amplifier and hydrophone receiver ends, reference optical wavelength intensity received, the full spectral signal, and accelerometer signals, all synchronized to the same timeline. From these data, nearly every scenario in the data acquisition sequence can be reconstructed. More sophisticated cloud-based QA diagnostics algorithms can then be developed by aggregative analysis of signal deviations.

C. Large Scale Distributed Learning to Improve Cancer Predictive Accuracy

Another design consideration is to include a touch screen interface to give the user limited access to software configuration such as entering racial/ethnic profile (or complexion), age range, breast density estimate, cup size, BMI, etc. Although some of the patient-specific factors currently do not enter the diagnostic model, they are potentially useful in later software release/updates as additional algorithm self-training codes are developed. For example, if a false-positive or false-negative diagnosis is generated, the user will be able to enter the correct diagnosis and force the algorithm to learn from the data. Similarly, correct diagnosis can be used by the self-learning codes in conjunction with patient-specific factors to discover statistically significant influence factors for increased diagnostic accuracy. In the future, if users consistently enter patient-specific factors and definitive tissue diagnoses associated with the SCS exam data, it is possible to improve the diagnostic accuracy continually by aggregating this information from multiple devices in the field. De-identified data can be transmitted to cloud-based applications that aggregate and disseminate statistically significant data to generate refined diagnostic models. Alternatively, if transmitting patient data to central repositories is culturally or administratively unacceptable, then downloadable "app" can be developed for the user to run model extraction algorithms. The app can be designed to bring in collective knowledge from other downloaded apps (i.e., app on other SCS devices in the field), extract and abstract diagnostic features, spectral fingerprints, etc., that may be significant in model building, and upload the abstracted data (not the patient data) to cloud-based servers.

Similarly to other large-scale distributed learning paradigms, it is anticipated that the predictive accuracy will continually improve with the frequency and variety of use. Importantly, it is envisioned that the SCS system be *adaptive* to population-specific signatures of cancer assay, with the ultimate goal of becoming a diagnostic and screening tool for global health.

V. CONCLUSION AND FUTURE WORK

Sono-contrast spectroscopy has been shown in preclinical and clinical studies to confer high discriminating power for diagnosing malignant breast masses. An adaptation strategy has been outlined to produce a portable device with uncompromised performance characteristics suitable for LMIC deployment. Additional use of modern wireless, cloud computing and large-scale distributed learning technologies will enable unprecedented cancer diagnosis algorithm's self-learning/adaptation and population-based tuning capabilities.

 ISBN: 978-1-61208-359-9

To further meet the cancer burden needs in LMICs, it is envisioned that a set of end-firing and side-firing probes incorporating the SCS technology will be developed for detecting cancers of the cervix, prostate and rectum. Pilot clinical studies will be designed to evaluate the effectiveness of SCS as either adjunct or primary detection technology in the presence/absence of standard screening tests.

ACKNOWLEDGMENT

The preclinical in vivo study and the pilot clinical study described in Sections II and III were carried out under the support of U.S. NIH/NCI grants R21 CA107860 and R33 CA107860, respectively.

REFERENCES

[1] http://www.who.int/cancer/detection/breastcancer/en/ World Health Organization webpage, accessed on March 24 2014.

[2] M. P. Coleman, M. Quaresma, F. Berrino, et al. "Cancer survival in five continents: A worldwide population-based study (CONCORD)". Lancet Oncol., vol. 9, August 2008, pp. 730-56.

[3] J. G. Elmore, K. Armstrong, C. D. Lehman, and S. W. Fletcher, "Screening for breast cancer". Journal of American Medical Association, vol. 293, October, 2005, pp. 1245-1256.

[4] M. Dyson, B. Woodward, and J. B. Pond, "Flow of red cells stopped by ultrasound". Nature, Vol. 232, 1971, pp. 572-573.

[5] B. A. Winey, V. Misic, L. Laio, K. Parker, B. M. Fenton, and Y. Yu, "In vivo cancer diagnosis with optical spectroscopy and acoustically induced blood stasis using a murine MCa35 model". Med Phys., vol. 33, June, 2006, pp. 1623-33.

[6] V. Misic, B. Winey, H. Liu, L. Liao, P. Okunieff, K. Parker, et al., "Tumor detection in vivo with optical spectroscopy". Conf. Proc. IEEE Eng. Med. Biol. Soc., vol. 5, May, 2005, pp. 4708-11.

[7] K. Yan, T. Podder, K. Huang, Y. Yu, and L. Liao, "A noninvasive multimodal sono-contrast NIR spectroscopy system for breast cancer diagnosis". BioInformatics and BioEngineering (BIBE), IEEE International Conference, 2010, pp. 285-286.

[8] K. Yan, T. Podder, K. Huang, L. Liao, and Y. Yu, "A multimodal sono-contrast NIR spectroscopy system for breast cancer diagnosis: System design and safety considerations". 3rd International Conference on Biomedical Engineering and Informatics (BMEI), 2010, pp. 1386-1390.

[9] F. L. Lizzi, D. J. Coleman, J. Driller, L. A. Franzen, and M. Leopold, "Effects of pulsed ultrasound on ocular tissue". Ultrasound Med. Biol., vol. 7, March, 1981, pp. 245-252.

[10] K. Yan, Y. Yu, and L. Liao, "A non-invasive multimodal sono-contrast NIR spectroscopy system for breast cancer diagnosis". 4th Int. Conf. Biomed. Eng. Informatics. 2011, pp. 1034-1037.

[11] K. Yan, Y. Yu, E. Tinney, R. Baraldi, and L. Liao, "Clinical study of a noninvasive multimodal sono-contrast induced spectroscopy system for breast cancer diagnosis". Med. Phys.; vol. 39, 2012, pp. 1571-8.

[12] K. M. Kelly, J. Dean, S. J. Lee, and W. S. Comulada, "Breast cancer detection: Radiologists' performance using mammography with and without automated whole-breast ultrasound". Eur Radiol. vol. 20, 2010, Nov., pp. 2557-64.

[13] K. Yan, Y. Yu, and L. Liao, "Multimodal sono-contrast NIR spectroscopy for breast cancer diagnosis: Cancer characterization modeling and subgroup study". IEEE ICSP2012 Proceedings October, 2012, pp. 2144-7.

 ISBN: 978-1-61208-359-9