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Low-Cost, Portable Optical Imaging Systems for Cancer Diagnosis

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Abstract

Worldwide incidence and mortality rates due to cancer continue to rise, with the burden of disease increasingly shifting to developing countries. Several optical diagnostic methods such as diffuse optical tomography, wide-field autofluorescence imaging, confocal microscopy, and optical coherence tomography, are currently under development to enable earlier detection of cancer. However, these are primarily intended for use in healthcare facilities in industrialized countries. Using knowledge gained from early clinical studies with these large-scale systems, we have designed and tested low-cost, portable versions of these instruments. We propose that these systems may be used for early diagnosis and screening in developing countries, and that pilot clinical studies are warranted in these low-resource settings.

I. Introduction

The global incidence of cancer is rising rapidly. It is estimated that in 2010, 60% of new cases worldwide will occur in the developing world [1]. As mortality rates due to infectious disease and childhood illnesses decline, life expectancies in developing countries will improve, leading to increases in incidence of many cancers. Adoption of Western lifestyle habits involving diet, exercise, and tobacco use may also contribute to this trend.

In the United States, it is well documented that early diagnosis of cancer is associated with improved prognosis [2]. For example, the mortality rates for colorectal cancer have declined by 4.7% per year between 2004-2004, compared to an annual decline of 1.8% for the period 1985-2002, a difference largely attributed to improvements in early detection and treatment of colorectal polyps. Figure 1 shows the 5-year survival rates for oral, esophageal, and cervical cancers, as a function of the stage at which the patient is diagnosed. In all cases, the long-term prognosis declines significantly when diagnosis is made at increasingly advanced stages. The size of each circle in the figure is proportional to the fraction of patients diagnosed with cancer at that stage, illustrating that for both oral and esophageal cancers, significant numbers of patients are identified with advanced stage disease. Clearly there is a pressing need to improve early screening methods for these cases, to detect cancerous and pre-cancerous lesions when treatment can be curative, considerably less expensive, and cause lower morbidity.

In the right-hand column of Figure 1, the data for cervical cancer appears more encouraging; most patients are diagnosed with early stage disease, which is associated with nearly 100% survival at 5-years. But this data is for the United States, where early detection of cervical cancer is largely due to widespread, effective screening with the Pap smear. In contrast, cervical cancer is the leading cause of death of any cancer for women in developing countries [3] where major screening programs are largely absent due to lack of financial

resources and clinical expertise. Providing access to quantitative, objective screening tools at the point-of-care can have significant impact on cancer morbidity and mortality in these settings, by enabling earlier diagnosis when treatment is cheaper and more effective[4].

Optical imaging technologies are well-suited to fill this need, based on collecting scattered or fluorescent light from tissue, and measuring changes in the amplitude, wavelength, and polarization state that result from the onset and progression of disease. Our group and others have developed both macroscopic “wide-field” [5-7,12,13] and microscopic “high-resolution” [8-10] optical imaging devices for cancer detection, evaluating large scale prototype systems in clinical studies at major referral centers in the United States. Having developed an understanding of the most diagnostically important imaging parameters in this earlier work [11], we have recently developed low-cost, portable, battery-powered versions of these systems, with the goal of providing appropriate tools to improve cancer screening and diagnosis in developing countries.

II. Methods

A. Macroscopic “wide-field” imaging

We have previously developed a wide-field imaging system for oral cancer detection [12], based on a modified Zeiss dental microscope. This instrument was designed to acquire images in cross-polarized white light, narrowband reflectance at four illumination wavelengths, and autofluorescence at four excitation wavelengths, in addition to conventional white light imaging. In a pilot clinical study comprising 56 patients with oral lesions, and 11 healthy subjects, the best diagnostic performance (in terms of the maximum area under the receiver-operator characteristic curve) was achieved by use of the ratio of red to green fluorescence emission intensities at 405 nm excitation [13]. The classification algorithm, based on linear discriminant analysis with the single input feature of red to green fluorescence ratio, demonstrated 100% sensitivity and 91.4% specificity for distinguishing normal from neoplastic tissue in an independent data set of 21 subjects.

We used this knowledge to develop a simplified wide-field imaging system (Figure 2a) that acquires images in cross-polarized white light and fluorescence at 405 nm excitation only. The system can be mounted on a surgical head mount, or a conventional tripod, and provides real-time image display on a laptop computer. Individual high-power LEDs are used for illumination of the tissue, with an orthogonally mounted polarizer and 435 nm long-pass filter mounted on a servo motor filter wheel in front of a compact color CCD camera for image acquisition. The system illuminates a 45 mm diameter field at a distance of 250 mm, with irradiance of 10 mW/cm² in autofluorescence mode.

B. Microscopic “high-resolution” imaging

Several techniques have been developed for *in vivo* microscopy, aimed at visualizing the morphological and functional features of neoplasia at the cellular level [8-10,14] to complement conventional histopathology. We previously developed a flexible, benchtop scanning confocal microscope, capable of imaging tissue specimens in fluorescence and reflectance modes, at 488 nm, 664 nm, and 784 nm wavelengths [15]. We and several other research groups have extended this confocal imaging technique to *in vivo* applications [8], and while high-quality images of sub-cellular detail can be obtained in living tissue, these systems typically require laser illumination, optomechanical scanning systems, photomultiplier tubes and associated power supplies. We recently developed a simple alternative system which can image sub-cellular detail in real-time [16], [17]. Based around wide-field epi-fluorescence imaging through a fiber optic bundle, our “high-resolution microendoscope” (HRME) shown in Figure 3 is contained within a 10“ × 8” × 2.5“ unit, and

is entirely battery-powered. When used with 0.01% (w/v) proflavine solution as a topical fluorescent contrast agent, a single LED source with center wavelength of 455 nm is used for excitation, with light delivered to and collected from the tissue via a flexible fiber-optic image guide. The proximal end of the fiber is imaged onto a compact CCD camera, with a 500-600 nm emission filter placed in the optical path to prevent reflected or backscattered light from reaching the detector. The current system generates images containing 1280×1036 pixels at 15 frames per second.

III. RESULTS

Images of the oral cavity acquired with the portable wide-field screening system are shown in Figure 4. In Figure 4a, the teeth are seen to be highly fluorescent, as is the underside of the tongue in this healthy subject, due primarily to stromal collagen. In Figure 4b, the characteristic loss of fluorescence is apparent as a darkened zone in the tissue above the teeth (arrows) of a patient presenting with a precancerous lesion at this site. This image was acquired in 125 ms, enabling the visualization of tissue autofluorescence at up to 8 frames per second.

A photograph of the fiber-optic probes used with the high-resolution microendoscope are shown in Figure 5a, with probes sized 0.5 mm and 1.0 mm in diameter alongside a miniature lens that can be affixed to the bundle to provide additional magnification. In Figure 5b, an image of normal human oral mucosa is presented, acquired *in vivo* with a 66 ms exposure time, again short enough to allow rapid, real-time visualization. Immediately following topical application of 0.01% proflavine solution, placement of the distal tip of the fiber bundle reveals bright labeled nuclei appearing as small dots uniformly distributed across the field of view. Figure 5c illustrates the characteristic morphology of the normal colonic mucosa, with regularly sized and spaced crypts outlined by brightly stained nuclei. The normal cervical epithelium is shown in Figure 5d, where again, small bright nuclei are apparent across the imaged field. Our previous *ex vivo* studies [16], [17] and current *in vivo* clinical studies have demonstrated that alterations in morphology at each of these organ sites are apparent under HRME imaging and correlated with neoplastic disease.

IV. DISCUSSION

Medical imaging continues to play a fundamental role in the management of cancer, ranging from screening and staging of disease, to providing surgical guidance and monitoring response to therapy. In industrialized countries, technologies such as MRI, CT, and PET are being developed and used to identify lesions through imaging of both structural and functional properties of tissue. However, access to this technology differs widely depending on geography and socioeconomic factors. A 2006 estimate placed the number of MRI machines in the US at around 11,000, with the first MRI machine installed in Malawi two years later (this single system is currently shared with neighboring Mozambique and Zambia). Even in developing countries with rapidly emerging economies such as India, there are only 0.5 MRI machines per million inhabitants, compared to 37 machines per million persons in the US [19].

Today, more than 70% of the world's cancer deaths occur in these low- to middle-income countries, with 80% of patients presenting with advanced disease at the time of diagnosis [21,22]. These figures are unlikely to be affected by a widespread infusion of high-level imaging technology in the foreseeable future. Even in developed countries, the presence of diagnostic imaging technology alone does not equate to widespread access. Patients in the US who are uninsured or who have Medicaid insurance are significantly more likely to be diagnosed with late stage cancer, and have significantly lower survival rates than patients

with private insurance [22]. At a time when the global incidence of cancer is rapidly increasing, there is an urgent need for effective and affordable tools and technologies to facilitate early detection, prevention, and treatment of cancer in low resource settings.

Optical imaging can be implemented in compact, robust, low-cost formats to address the crucial need for improved cancer screening within this context. In the screening setting, the healthcare provider typically inspects a large tissue area or whole organ at the *macroscopic* level, with the goal of detecting any abnormal regions. Wide-field imaging can potentially aid the non-specialist provider in finding these suspicious sites with high diagnostic sensitivity, however, such techniques are vulnerable to confounding factors such as inflammation, which can reduce specificity. By inspecting these suspicious sites with *microscopic* level resolution, it may be possible to distinguish benign from malignant conditions and simultaneously achieve high sensitivity *and* specificity.

We have presented both wide-field (macroscopic) and high-resolution (microscopic) optical imaging systems which can detect anatomical, morphological, and functional indicators of neoplasia. We are evaluating their diagnostic performance in ongoing pilot clinical studies [16], [17]. These systems were assembled for under \$4000 each and are portable, robust, and battery-powered, all features which may lead to increased access to enhanced cancer screening tools in low-resource settings.

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Fig. 1. 5-year relative survival rates for oral, esophageal, and cervical cancers, as a function of stage at diagnosis. The area of each circle is proportional to the fraction of patients diagnosed at that particular stage. Data from [2].

Fig. 2.

- (a) Schematic illustration of the wide-field imager designed for evaluation of the oral cavity.
(b) Evaluation of the system at a clinic in Mumbai, India.

Fig. 3.

(a) Schematic diagram of the high-resolution microendoscope. (b) Photograph of the assembled system, contained in a portable, battery-powered unit measuring $10'' \times 8'' \times 2.5''$.

Fig. 4.
(a) Wide-field fluorescence imaging of the normal oral cavity, illustrating characteristic bright fluorescence from the teeth and underside of the tongue. (b) Image of a precancerous lesion above the teeth, with loss of autofluorescence in the region indicated by arrows.

Fig. 5.

(a) Photograph of the flexible fiber-optic probes used with the high-resolution microendoscope (1&2), alongside a miniature lens assembly (3). Images of normal human tissues, acquired *in vivo* with the 1.0 mm diameter probe, from the oral mucosa (b), colon (c), and cervix (d). Cell nuclei appear as bright dots within the 750 μm diameter field of view.