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TOPIC HIGHLIGHT

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Role of optical spectroscopy using endogenous contrasts in clinical cancer diagnosis

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Abstract

Optical spectroscopy has been intensively studied for cancer management in the past two decades. This review paper first introduces the background of optical spectroscopy for cancer management, which includes the advantages of optical techniques compared to other established techniques, the principle of optical spectroscopy and the typical setup of instrumentation. Then the recent progress in optical spectroscopy for cancer diagnosis in the following organs is reviewed: the brain, breast, cervix, lung, stomach, colon, prostate and the skin. Reviewed papers were selected from the PubMed database with keywords combining the terms of individual optical spectroscopy techniques and cancers. The primary focus is on the *in vivo* applications of optical spectroscopy in clinical studies. *Ex vivo* studies are also included for some organs to highlight special applications or when there are few *in vivo* results in the literature. Practical considerations of applying optical spectroscopy in clinical settings such as the speed, cost, complexity of operation, accuracy and clinical value are discussed. A few commercially available clinical instruments that are based on optical spectroscopy techniques are presented. Finally several technical challenges and standard issues are discussed and firm conclusions are made.

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Key words: Cancer diagnosis; Clinical oncology; Endogenous contrasts; Optical spectroscopy

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INTRODUCTION

Optical spectroscopy for cancer diagnosis has been a hot research area over the past two decades. This paper will review several popular optical spectroscopy techniques including diffuse reflectance spectroscopy, fluorescence spectroscopy and Raman spectroscopy, which are based on interrogating endogenous optical contrasts in tissues. Several other promising optical spectroscopy techniques such as light scattering spectroscopy[1], coherent backscattering spectroscopy[2], and low coherence spectroscopy[3], are not included because they are relatively less studied in clinical applications. Reviewed papers were selected from the PubMed database with keywords combining the terms of individual optical spectroscopy techniques and cancers.

This paper first introduces the background of optical spectroscopy for cancer management, which includes the advantages of optical spectroscopy techniques compared to other established techniques, the principle of optical spectroscopy and the typical setup of instrumentation.

The recent progress of optical spectroscopy for cancer diagnosis in the following organs is then reviewed, which includes the brain, breast, cervix, lung, stomach, colon, prostate and the skin. The practical considerations of applying optical spectroscopy in clinical settings such as the speed, cost, complexity of operation, accuracy and clinical value are discussed, in which several commercially available clinical instruments based on optical spectroscopy techniques are also presented. Finally several technical challenges and standard issues are discussed, and the conclusions are made.

BACKGROUND IN OPTICAL SPECTROSCOPY FOR TISSUE CHARACTERIZATION

Advantages of optical techniques in clinical oncology compared to other established modalities

Optical spectroscopy and imaging techniques have emerged as promising alternative or adjunct tools to other established imaging modalities in clinical oncology such as ultrasonography, X-ray computed tomography (CT) and magnetic resonance imaging (MRI) in recent years. Tremendous growth has been achieved in the past three decades. Compared to these established imaging modalities, optical techniques possess several unique advantages that make them particularly attractive in clinical cancer management.

First, optical irradiation is non-ionizing, thus, does not present a health hazard even for a relatively long exposure time. Thus, optical measurements can be repeated as necessary. Second, optical measurements are sensitive to biochemical and morphological changes associated with carcinogenesis through the interaction between light and endogenous molecules in tissues. Third, technical advances in light sources and detectors have made it practical to achieve real time, or close to real time, optical measurements in many situations. Although the penetration depth of light is in general considered to be small as compared to X-ray or ultrasound, the sensing depth of optical measurements can actually be varied from a few hundred micrometers to several centimeters by tuning light wavelengths and manipulating source-detector configuration[4]. The tunable sensing depth adds extra flexibility and sensitivity for those special clinical scenarios. Last but not least, the development of fiber-optic probes and miniaturized detectors has made it feasible to incorporate optical spectroscopy into commercial endoscopy systems to reach internal organs.

Principles of optical spectroscopy for cancer diagnosis

The basis of optical spectroscopy for tissue characterization is built upon various light-tissue interactions including absorption, scattering and fluorescence. In the following paragraphs, how the three basic light-tissue interactions contribute to detected optical signals and how the optical signal can be used for cancer diagnosis will be described.

Absorption refers to the phenomenon in which a molecule absorbs excitation light photons without emitting new photons. The major light absorber in tissues is hemoglobin in the whole optical spectrum[5]. Total hemoglobin concentration reflects the degree of vascularization, which can be useful in examining angiogenesis during cancer development. The absorption spectrum of hemoglobin can change with its degree of oxygenation. Therefore, hemoglobin oxygenation is another important parameter that can affect tissue absorption in addition to total hemoglobin concentration. As hemoglobin is the oxygen carrier present in human blood, the variation in hemoglobin oxygenation could indicate the change in the balance between oxygen demand and oxygen supply in tissues. Water and lipid can absorb near-infra-red light. Previous studies have demonstrated that water and lipid contents are significantly different between normal breast tissue and breast cancer[6].

Scattering refers to the phenomenon in which a photon is deflected from the incident direction after interacting with a molecule in the tissue. There are two types of scattering in general, i.e. elastic scattering and inelastic scattering. Elastic scattering is a type of scattering that occurs without a frequency change from the incident photon to the scattered photon, which is also called Raleigh scattering. Major tissue elastic scatterers include nuclei, mitochondria and collagen fibers[7]. Elastic scattering has been shown to be effective in detecting epithelial pre-cancers[8,9] because of the changes in nuclei size, nucleus-to-cytoplasm ratio and the density of collagen fibers in cancer cells. Inelastic scattering refers to the scattering type in which a frequency change occurs. Depending on whether the frequency of scattered photons decreases or increases, inelastic scattering is called Stokes Raman scattering (frequently just Raman scattering) or anti-Stokes Raman scattering[10]. Raman scattering will be covered in this paper as the fundamental phenomenon behind Raman spectroscopy. However, anti-Stokes Raman scattering will not be touched because it is much less explored in clinical settings. Raman scatterers in tissues include cell cytoplasm, cell nucleus, fat, collagen, cholesterol-like lipid deposits and water[11].

Fluorescence refers to the emission of light that results from the return of a molecule from a singlet excited state to the ground state. Due to energy loss in the process, the emission wavelength is always longer than the excitation wavelength. The fluorophore refers to those molecules exhibiting fluorescence when illuminated by light at certain wavelengths. Fluorescence light emitted from fluorophore molecules is subject to absorption and scattering when propagating in tissues, which could induce difficulty in the interpretation of fluorescence spectra. The most extensively studied fluorophore molecules are reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FAD). These two molecules are metabolic coenzymes involved in the reduction-oxidation process to produced energy for cellular activities. The fluorescence contributed by these two fluorophores has been explored to estimate redox ratios to reflect the variation in the metabolic rate of tissues[12].

Table 1 lists primary absorbers and scatterers; while Table 2[13] tabulates endogenous fluorophores and their peak excitation and emission wavelengths.

Diffuse reflectance spectroscopy measures light inten-

Table 1 Primary absorbers and scatterers present in tissues

Light-tissue interaction	Source
Absorption	Hemoglobin, β-carotene, water, lipid
(Raleigh) scattering	Nuclei, mitochondria, collagen fibers
Raman scattering	Cell cytoplasm, cell nucleus, fat, collagen, cholesterol-like lipid deposits and water

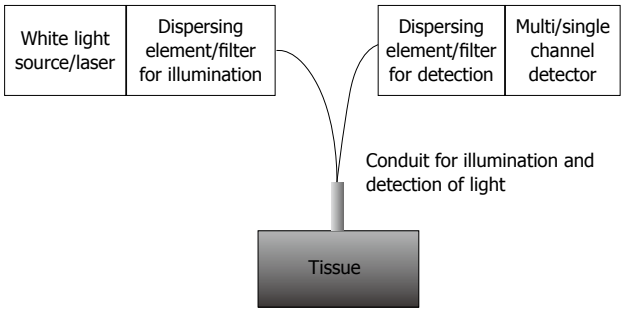

Figure 1 A general schematic of a fiber-optic system for optical spectroscopy.

sity at the excitation wavelengths. Measured diffuse reflectance spectra are sensitive to the absorption and scattering properties of tissues. Fluorescence spectroscopy measures fluorescence light intensity at the emission wavelengths that are longer than the excitation wavelength. Measured fluorescence light is subject to the effect of light absorption and scattering especially when the sensing volume is large. Raman spectroscopy measures Raman light intensity at the wavelengths longer than the excitation wavelength, but the wavelength range of detected Raman light is typically smaller than that in fluorescence spectroscopy. Detected Raman spectra are also subject to the effect of light absorption and scattering.

Instrumentation

A general schematic of a fiber-optic optical spectroscopy system for point measurements[14] is shown in Figure 1. This system consists of a light source (a white light source or laser), a dispersing element or band-pass filter for selection of illumination wavelengths, a conduit for delivery of illumination light and collection of emitted light, a dispersing element or band pass filter for selection of emission wavelengths, and a single-channel or multi-channel detector for measurement of signal intensities at the wavelengths of interest.

The fiber-optic probe is often used as the conduit for delivery of illuminating light and collection of emitted light[15]. A fiber-optic probe is usually a metal cylindrical tube with one or multiple optical fibers assembled in it. Some fibers are used for delivering light onto the tissue surface; the same fibers or other fibers depending on the probe design are used for collecting light emanating from the tissue surface.

In diffuse reflectance spectroscopy and fluorescence spectroscopy, a white light source such as xenon lamp is frequently used to provide a large range of wavelengths.

Table 2 Primary endogenous fluorophores, their peak excitation-emission wavelength pairs and location in human epithelial tissues[13]

Category of fluorophores	Endogenous fluorophores	Peak excitation-emission wavelength pair (nm)	Primary tissue location
Structural protein	Collagen	325-400	Stroma
Electron carrier	FAD	450-535	Cells
	NADH	351-460	Cells
Amino acid	Tryptophan	280-350	Proteins

FAD: Flavin adenine dinucleotide; NADH: Reduced nicotinamide adenine dinucleotide.

Various lasers can also be used when the excitation light with high power is needed. The dispersing element for illumination is typically a monochromator and sometimes there is no dispersing element which is called broadband illumination. The dispersing element for detection can be a monochromator, which is often followed by a single-channel detector such as a photomultiplier tube (PMT). Alternatively, the dispersing element can be a spectrograph, which is followed by a multi-channel detector such as a charge coupled device (CCD). This configuration enables rapid measurements of optical spectra, but frequently at the cost of lower sensitivity to light at certain wavelengths as compared to the configuration of single-channel detectors.

In Raman spectroscopy, the excitation light is typically provided by a high power laser because of weak Raman signals. A laser line filter, which transmits laser light while suppressing ambient light, is frequently used to clean excitation light. In the detection module, a long pass filter is used to remove excitation light. Then a spectrograph disperses Raman light of various wavelengths at different spatial locations, which are then mapped onto a CCD to achieve rapid measurements. The laser line filter and the long pass filter could be mounted at the tip of the illumination fibers and the detector fibers in the probe to reduce the background Raman signal from fibers.

OPTICAL SPECTROSCOPY TECHNIQUES IN CLINICAL CANCER DIAGNOSIS

While optical spectroscopy may play an important role in many aspects of clinical cancer management such as cancer screening in the breast[16,17], cervix[18,19], oral cavity[20], and treatment planning and monitoring in the brain[21], breast[22] and the prostate[23,24], emphasis will be placed on cancer diagnosis due to the following reasons: First, cancer diagnosis appears to be the most frequently cited goal in relevant publications. Second, the optical techniques developed for cancer diagnosis are in general also applicable to cancer screening and treatment planning as well as outcome evaluation.

In this literature review, the preference will be given to *in vivo* clinical studies. *Ex vivo* or *in vitro* studies are sometimes mentioned to highlight specific applications. No preclinical studies will be included. The review will be organized in terms of organ sites, which cover the brain,

breast, cervix, lung, stomach, colon, prostate and the skin. For each organ site, a brief description of the state of the art is presented, followed by representative studies.

Brain

Diffuse reflectance spectroscopy in the near infra-red (NIR) spectrum, sometimes named NIR spectroscopy, has attracted much attention in brain imaging since the 1990s, because of the relatively large penetration depth of NIR light. It was found feasible to detect brain activities through intact skulls[25] especially in children. The major physiological parameters extracted from NIR spectroscopy include total hemoglobin concentration and tissue oxygenation. Because of weak scattering in this range, light transport in this region can be described by an analytical expression, i.e. diffuse theory, which greatly facilitates data analysis. This technique is frequently used in an imaging modality, i.e. diffuse optical tomography (DOT). Multiple detectors are used to reconstruct three-dimensional images of cerebral hemodynamics. For a review of DOT imaging in the brain, please refer to Jacobs *et al*[26], Gibson *et al*[27], and Huppert *et al*[28]. However, because most brain cancers in an intact skull are not within the reach of light, this technique is less studied in clinical oncology.

Diffuse reflectance spectroscopy in the visible spectrum and fluorescence spectroscopy have been studied in tumor margin assessment or tissue characterization during neurosurgery procedures. Compared to NIR spectroscopy, diffuse reflectance spectroscopy in the visible spectrum and fluorescence spectroscopy possess higher chemical sensitivity. The problem of small penetration depth associated with ultraviolet and visible light is no longer an issue during surgery, which opens a new venue to apply optical spectroscopy in brain cancer management. For a review on the neuro-oncological applications of optical spectroscopy, please refer to Toms *et al*[29]. A few representative studies were briefly reviewed below.

Lin *et al*[30] investigated the applicability of combined autofluorescence and diffuse-reflectance spectroscopy for intraoperative detection of infiltrating tumor margins (ITM) in a pilot *in vivo* clinical trial consisting of 26 brain tumor patients. A two-step empirical discrimination algorithm yielded a sensitivity and specificity of 100% and 76%, respectively, in differentiating ITM from normal brain tissues.

Antonsson *et al*[31] investigated the use of diffuse reflectance spectroscopy for differentiating tissue types to improve intracerebral guidance during deep brain stimulation. Diffuse reflectance spectroscopy measurements in 10 patients were recorded for three different functional targets including the subthalamic nucleus (STN), internal globus pallidus (GPi) and zona incerta (Zi). Significant intensity differences between white and gray matter were found to be at least 14% ($P < 0.05$) and 20% ($P < 0.0001$) for MRI and spectral-sorted data, respectively.

Lin *et al*[32] further investigated the feasibility of using diffuse reflectance and fluorescence spectroscopy to differentiate pediatric neoplastic and epileptogenic brain from normal brain in an *in vitro* study. Statistically significant differences ($P < 0.01$) were found between (1) neoplastic brain and normal gray matter; (2) epileptogenic brain and normal gray matter; and (3) neoplastic brain and normal white matter.

Krafft *et al*[33] explored the use of Raman spectroscopic mapping for distinguishing between normal brain tissue and gliomas and meningiomas. *Ex vivo* tissues were examined by a Raman spectrometer with 785 nm excitation coupled to a microscope. Normal brain tissue was found to contain higher levels of lipids, intracranial tumors have more hemoglobin and lower lipid to protein ratios, meningiomas contain more collagen with maximum collagen content in normal meninges.

Breast

Breast cancer is perhaps the most extensively studied cancer in the community of biomedical optics. Optical spectroscopy techniques have been explored in a variety of forms in breast cancer diagnosis, including non-invasive breast cancer imaging, tumor characterization for margin assessment during breast surgery and "optical biopsy" measurements in needle biopsy or fine needle aspiration procedures.

Non-invasive breast cancer imaging can be performed in diffuse optical tomography[34,35] or diffuse reflectance spectroscopy often in the frequency domain[6,36]. Multiple wavelengths are used to achieve spectroscopic measurements and provide functional images of the breast, which include hemoglobin concentration, oxygen saturation, water and lipid content as well as scattering properties. Although this approach sounds attractive, it suffers from low spatial resolution due to multiple light scattering. To tackle this problem, other imaging modalities such as CT and MRI were proposed to provide anatomical images at a high spatial resolution[35,37,38], which is incorporated into the DOT reconstruction algorithm to combine with the functional images obtained in DOT. Because of the advantage in the signal to noise ratio, optical equipment in the frequency domain is preferred in many cases. For a more detailed review of this technique, please refer to publications[35,39,40]. Shah *et al*[36] and Tromberg *et al*[16] have provided excellent discussion on the potential roles of optical spectroscopy in the clinical management of breast cancer.

Tumor margin assessment during open surgery using optical spectroscopy has been reported by several groups[41-44] as summarized in Table 3. It is worth noting that the accuracy changes with the classification algorithm[41] which suggests the importance of selecting appropriate data analysis methods. There is a special case[42] in which Raman spectroscopy detected a grossly invisible cancer that was confirmed by pathologic review. This finding gave the patient a chance for a second surgical procedure to prevent the recurrence of cancer.

All these previous studies demonstrated that optical spectroscopy could be used in a real-time fashion to guide tissue excision during breast surgery, potentially to reduce the need for repeated surgery resulting from positive margins, and thereby reducing the recurrence rate of breast cancer following mastectomy surgery.

Needle biopsy has become another popular carrier of fiber-optic probes for performing optical spectros-

Table 3 Summary of techniques, patient population and accuracy in previous optical spectroscopy studies for intraoperative breast margin assessment

Author	Techniques	Patient population	Accuracy
Bigio *et al*[41]	Elastic-scattering spectroscopy (a special diffuse reflectance spectroscopy)	31 women, a total of 72 histology sites in breast tissue	Sensitivities of 69% and specificities of 85% for breast tissue
Haka *et al*[42]	Raman spectroscopy	9 patients undergoing partial mastectomy procedures	Accuracy of 100% for carcinoma; accuracy of 93.3% for distinguishing cancerous from normal and benign tissues
Ramanujam *et al*[43]	Diffuse reflectance spectroscopy in spectral imaging	55 margins in 48 patients.	Sensitivity of 79% and specificity of 67% for detection of residual tumor, with an 89% sensitivity for ductal carcinoma *in situ* alone
Keller *et al*[44]	Autofluorescence and diffuse reflectance spectroscopy and spectral imaging	145 normal spectra were obtained from 28 patients, and 34 tumor spectra were obtained from 12 patients	Differentiate normal tissue or tumor with 85% sensitivity and 96% specificity

copy, which is technically called "optical biopsy". The advantages of "optical biopsy" compared to physical biopsy are not only non-invasiveness and high accuracy but also an increased sensing tissue volume, which could greatly reduce the chance of missing hidden cancer sites. Manoharan *et al*[45] performed an early study to picture the possibility of incorporating Raman spectroscopy into a biopsy needle for breast cancer examination. Bigio *et al*[41] performed transdermal-needle measurement using elastic scattering spectroscopy for instant diagnosis with minimal invasiveness for breast tissue examination. The accuracy of transdermal-needle measurements combined with spectral measurements in open surgery is reported in Table 3.

van Veen *et al*[46] performed differential path-length spectroscopy (DPS), which is essentially a type of diffuse reflectance spectroscopy, on healthy and malignant breast tissue using a fiber-optic needle probe. A special tissue model was used to yield information on the local tissue blood content, the local blood oxygenation, the average micro-vessel diameter, the beta-carotene concentration and the scatter slope. The histological outcome of core-needle biopsies taken from the same location was used as the gold standard. Malignant breast tissue has a smaller tissue oxygenation and a higher blood content compared to normal breast tissue.

Yu *et al*[47] developed a side-firing fiber-optic sensor based on near-infrared spectroscopy for guiding core needle biopsy diagnosis of breast cancer. The sensor is inserted into a core biopsy needle to measure diffuse reflectance spectra in the NIR spectrum at the biopsy site through an aperture on the needle before the tissue is removed for histology. Preliminary *in vivo* measurements were performed on 10 normal or benign breast tissues from 5 women undergoing stereo- or ultrasound-guided core needle biopsy and showed good correlation with histopathology.

Zhu *et al*[48] explored the use of fluorescence spectroscopy for guiding breast biopsies. A total of 121 biopsy samples with accompanying histological diagnosis were obtained clinically. The statistical data analysis provided a cross-validated sensitivity and specificity of up to 81% and 87%, respectively, for discrimination between malignant and fibrous/benign samples, and up to 81% and 81%, respectively, for discriminating between malignant and adipose samples. The corresponding receiver operator curves (ROC) yielded an area under the curve (AUC) of 0.87 and 0.84 in two cases. It is noted that ROC is a graph of sensitivity against (1-specificity) and the AUC is an indicator of the diagnostic performance.

In these applications, quantitative methods have been developed in all optical spectroscopy techniques, which provide extra information to elucidate the biochemical basis of carcinogenesis in the breast in addition to its use for diagnosis. For instance, diffuse reflectance spectroscopy has been used to derive vascular oxygenation and total hemoglobin content in breast cancer[5]. Raman spectroscopy was used to derive information on cholesterol-like lipid deposits, fat, collagen, and cell nucleus/cytoplasm[42].

Cervix

Because of relatively easy access to the cervix, numerous studies[14,49-51] have been reported on the *in vivo* diagnostics of cervical neoplasia. Cardenas-Turanzas *et al*[52] presented an excellent review on the clinical effectiveness of diffuse reflectance and fluorescence spectroscopy for the *in vivo* diagnosis of cervical intraepithelial neoplasia. According to this review, optical spectroscopy showed a similar performance to colposcopy and can be an effective adjunct to colposcopy to help localize lesions. It also has potential use in cervical screening or to triage patients on Pap smear.

The following review papers may also be helpful. Murali Krishna *et al*[51] provided a brief overview on the optical spectroscopic approach to cervical cancer diagnosis as well as on radiation therapy and radiation resistance. Bazant-Hegemark *et al*[53] reviewed several tools capable of non-destructive mapping of the cervix at high resolution in a clinical environment including infrared spectroscopy and Raman spectroscopy in terms of clinical performance for diagnosis. Drezek *et al*[54] presented an overview of various optical techniques including optical spectroscopy for the detection of precancerous lesions in the uterine cervix presented at the Second International Conference on Cervical Cancer. This review strong recommends the use of the Littenberg method for assessing new techniques to ensure that better technologies will stand out.

Several studies reported on the quantification of physiological parameters based on measured optical spectra,

which provided insight into the development of cervical dysplasia at various stages. Chang *et al*[55] used an analytical model to estimate the contributions of several optical biomarkers by analyzing spectra from diffuse reflectance spectroscopy and fluorescence spectroscopy measurements. The model was applied to 493 *in vivo* fluorescence measurements of cervical tissue acquired from 292 patients. The results show an increase in epithelial flavin adenine dinucleotide (FAD) fluorescence, a decrease in epithelial keratin fluorescence, an increase in epithelial light scattering, a decrease in stromal collagen fluorescence, and an increase in stromal hemoglobin light absorption in dysplastic tissue compared to normal tissue. These changes likely reflect an increase in the metabolic activity and loss of differentiation of epithelial dysplastic cells, and stromal angiogenesis associated with dysplasia.

Chang *et al*[56] assessed the capability of a diffuse reflectance spectroscopy technique to identify contrasts in optical biomarkers at different grades of cervical intraepithelial neoplasia (CIN) using a numerical model. In a total of 89 sites examined in 38 patients, there were 46 squamous normal sites, 18 CIN 1 sites, and 15 CIN 2(+) sites. Total hemoglobin was statistically higher in CIN 2(+) compared with normal and CIN 1 sites, which was attributed to stromal angiogenesis. Scattering was significantly reduced in CIN 1 and CIN 2(+) compared with normal sites, which was attributed to breakdown of the collagen network in the cervical stroma.

Lung

Typical optical spectroscopy equipment can be readily used for characterization of tissue biopsies from the lung[57-59]. Huang *et al*[59] used a near-infrared (NIR) Raman spectroscopy system at 785 nm excitation to measure bronchial tissue specimens including 12 normal specimens, 10 squamous cell carcinoma (SCC) and 6 adenocarcinoma specimens obtained from 10 patients. They demonstrated that Raman spectra differed significantly between normal and malignant tumor tissue, with tumors showing higher percentage signals for nucleic acid, tryptophan and phenylalanine and lower percentage signals for phospholipids, proline and valine, compared to normal tissue.

Yamazaki *et al*[58] constructed a near-infrared multichannel Raman system with an excitation wavelength at 1064 nm. They collected a total of 210 Raman spectra. The resulting sensitivity of cancer prediction was up to 91% and the specificity was 97% with an error margin of $P < 0.0001$ according to Fisher's exact test.

Aerts *et al*[57] successfully related HIF1a, which is one of the hypoxia-related proteins, to *in vivo* spectroscopic measurements of tumor blood saturation performed during bronchoscopy in 17 tissue samples. There was a significant difference in the spectroscopically determined saturations between the biopsies with negative expression of HIF1a and the biopsies with positive expression of HIF1a ($P < 0.005$).

Optical spectroscopy can also be incorporated into a commercial endoscopy system to perform *in vivo* examinations of the lung. Zeng *et al*[60] developed an integrated endoscopy system for simultaneous imaging and spectroscopy to detect early lung cancers. Zeng *et al*[61] proposed to use autofluorescence imaging and white light reflectance imaging to obtain high diagnostic sensitivity, while at the same time using non-contact point reflectance/fluorescence spectroscopy to reduce false positive biopsies. A pilot clinical study involving 22 lung patients demonstrated that the malignant lung lesions can be differentiated from the benign lesions using this system with a sensitivity and specificity of more than 80%.

Stomach

Numerous studies have reported on the examination of *ex vivo* stomach tissue samples using optical spectroscopy. Kawabata *et al*[62] performed Raman spectroscopy measurements on 251 fresh biopsy specimens obtained from 49 gastric cancer patients. Fresh specimens were measured with an excitation wavelength of 1064 nm. A sensitivity of 66%, a specificity of 73%, and an overall accuracy of 70% were achieved for the differentiation of gastric carcinoma from normal mucosa. Teh *et al*[63] applied near-infrared (NIR) Raman spectroscopy at 785-nm excitation in a total of 73 gastric tissue samples (55 normal, 18 cancer) from 53 patients. The predictive sensitivity and specificity of the independent validation dataset were 88.9% and 92.9%, respectively, for separating cancer from normal samples.

Given the high chemical specificity of Raman spectroscopy, it can be used to find the source of Raman signals contributing to cancer diagnosis. Teh *et al*[64] measured Raman spectra of 88 gastric tissue samples from 56 patients. Significant differences in Raman spectra were observed among normal, *Helicobacter pylori* infection (*Hp*-infection) and intestinal metaplasia (IM) gastric tissue, which were attributed to proteins, lipids and porphyrin. Data analysis yielded diagnostic sensitivities of 91.7%, 80.0%, and 80.0%, and specificities of 80.0%, 100%, and 92.7%, respectively, for the classification of normal, Hp-infection and IM gastric tissues. Raman spectroscopy has also been used in the early diagnosis and typing of intestinal and diffuse adenocarcinoma of the stomach[65], in which predictive accuracies of 88%, 92% and 94% were achieved for normal stomach, and intestinal- and diffuse-type gastric adenocarcinomas, respectively.

Optical spectroscopy has been incorporated into endoscopy systems for *in vivo* measurements of stomach cancer. Mayinger *et al*[66] evaluated light-induced autofluorescence spectroscopy in a commercial endoscopy system for the *in vivo* diagnosis of gastric cancer. A total of 15 patients with pure adenocarcinoma and 16 patients with gastric cancer containing signet-ring cells were recruited into the study. A sensitivity of 84% and a specificity of 87% were obtained for the diagnosis of pure adenocarcinoma of the stomach. The diagnostic performance was found to decrease with increasing numbers of signet-ring cells and tumor grade.

Colon

Some optical spectroscopy techniques such as diffuse reflectance spectroscopy have been incorporated into colonoscopy[67] or flexible sigmoidoscopy[68] to perform *in vivo*

measurements. Dhar *et al*[69] assessed the diagnostic potential of elastic scattering spectroscopy, which is essentially a particular type of diffuse reflectance spectroscopy, in colonoscopy to differentiate abnormal colon tissues *in vivo*. A total of 483 spectra (290 normal, 19 hyperplastic, 69 adenomatous polyps, 74 chronic colitis, and 31 colorectal cancer) were obtained from 138 sites in 45 patients at colonoscopy. The sensitivity and specificity of differentiating adenomas from hyperplastic polyps, cancer from adenomatous polyps, colitis from normal tissue, dysplastic mucosa (from polyps) from colitis were 84% and 84%, 80% and 75%, 77% and 82%, 85% and 88%, respectively.

Zonios *et al*[70] first analyzed diffuse reflectance spectra collected from adenomatous colon polyps and normal colonic mucosa of patients undergoing colonoscopy to estimate the following four parameters: hemoglobin concentration, hemoglobin oxygen saturation, effective scatterer density, and effective scatterer size. It was observed that normal and adenomatous tissue sites exhibited differences in hemoglobin concentration and effective scatterer size, which were in agreement with other studies that employed standard methods. A similar method was used by Wang *et al*[67] to quantify total hemoglobin concentration (THC) and oxygen saturation (StO_2) *in vivo* in 27 patients with colorectal cancer (CRC). Increased hemoglobin concentration and decreased oxygenation were observed from normal sites to premalignant tissues and then to malignant tissues.

Roy *et al*[68] incorporated polarization-gated spectroscopy into flexible sigmoidoscopy to detect an early increase in blood supply (EIBS) in the endoscopically normal rectum (n = 366). The rectal mucosal oxyhemoglobin content in females with advanced proximal neoplasia (n = 10) was significantly higher than that in the control group. It is worth noting that the addition of rectal oxyhemoglobin information dramatically increased the sensitivity to advanced neoplasia compared to flexible sigmoidoscopy alone. The sensitivity and specificity were 100% and 76.8%, respectively.

The research in Raman spectroscopy has been mostly limited to *ex vivo* studies likely due to the technical difficulty in obtaining Raman spectra at a reasonable signal to noise ratio. Stone *et al*[71] carried out Raman measurements for optical diagnostics in various organs including colon using an optimized commercial Raman microspectrometer. Both the sensitivity and the specificity were greater than 90% for all tissues. Widjaja *et al*[72] combined near-infrared (NIR) Raman spectroscopy at 785 nm excitation with support vector machines (SVM) for the classification of different histopathological groups in colon tissues. A total of 105 colonic tissue specimens from 59 patients including 41 normal, 18 hyperplastic polyps and 46 adenocarcinomas were included in this study. The results showed that the maximum overall diagnostic accuracy ranged from 98.4% to 99.9%. Beljebbar *et al*[73] used near-infrared Raman microspectroscopic imaging to investigate the changes in composition from normal colonic tissues to adenocarcinoma *ex vivo*. Multivariate statistical analysis was applied to the Raman spectra to identify the molecular composition and distribution of lipids, proteins, mucus and collagens in normal and malignant tissue. The results matched those of conventional histopathological examination.

Blood plasma has been also used as samples for optical measurements. Fluorescence spectroscopy in blood has been exploited by Lualdi *et al*[74] to diagnose colorectal cancer. The study involved 341 subjects including 169 normal blood donors. Plasma fluorescence spectrum was measured in all subjects. The fluorescence emission peak around 615-635 nm was assigned to endogenous porphyrin. The peak intensity was significantly different between patients bearing colorectal cancer and normal blood donors. The ROC analysis resulted in an area under the curve of 0.72, close to that reported for the carcinoembryonic antigen (CEA) test, which suggests that this method could be a cost effective alternative screening test to CEA.

Dekker *et al*[75] and Wallace *et al*[76] reviewed recent advances in colonic imaging, which included various optical imaging techniques. Many of these optical imaging techniques, such as fluorescence imaging and narrow-band imaging, are essentially the extension of optical spectroscopy techniques, in which only the data at a few discrete wavelengths are acquired at many pixels. Moglia *et al*[77] reviewed another exciting *in vivo* imaging technique, capsule endoscopy, which enables remote diagnostic inspection of the gastrointestinal tract without sedation and with minimal discomfort.

Prostate

Various optical spectroscopy techniques have been explored for the study of *ex vivo* prostatic tissue samples, and these have provided the basis for future *in vivo* studies. Because the prostate is a solid organ and light typically cannot penetrate the whole organ, optical spectroscopy techniques would have to be incorporated into biopsy needles or applied during prostatectomy to be useful. Sharma *et al*[78] reported the development of a needle like, bifurcated, fiber-optic probe for diffuse reflectance spectroscopy measurements in human prostate cancer. The results from 23 prostate specimens demonstrate that the derived hemodynamic parameters and optical properties can serve as good biomarkers to differentiate tumor tissue from normal tissue in the human prostate.

Crow *et al*[79] employed a fiber-optic Raman system to differentiate between benign and malignant bladder and prostate pathologic findings *in vitro*, in which a total of 197 Raman spectra were recorded from 38 snap-frozen prostate samples collected at transurethral resection of the prostate. An overall accuracy of 86% was reported for differentiation of benign prostatic hyperplasia and prostatitis from prostate cancer.

The combination of multiple complementary techniques has been reported to improve prostate cancer detection. Salomon *et al*[80] combined laser-induced autofluorescence, white-light remission, and high-frequency impedance spectroscopy in an *ex vivo* study. Ninety-five frozen tissue samples from 32 patients undergoing radical prostatectomy for clinically localized prostate cancer were thawed for data acquisition. The statistical analysis of laser-induced autofluorescence and white-light remis-

sion data demonstrated a differentiation of benign and malignant prostate tissue with a sensitivity of 87.5% and a specificity of 87.3%. By adding the acquired high-frequency impedance data to the statistical analysis, sensitivity and specificity were increased to 93.8% and 92.4%.

Interstitial photodynamic therapy (PDT) in prostate cancer has been intensively studied. This therapy is particularly suited to the prostate because of its capability of precise delivery of light dosage and minimum damage to surrounding vital organs. Optical spectroscopy techniques have been shown to be valuable in monitoring relevant light and tissue parameters for the optimization of PDT outcome. Zhu *et al*[81] quantified the distribution of light fluence rate, optical properties, drug concentration, and tissue oxygenation for PDT of prostate cancer using diffuse reflectance spectroscopy and fluorescence spectroscopy before and after PDT treatment. This study shows significant inter- and intra-prostatic variations in tissue optical properties and drug distribution, which suggests that a real-time dosimetry measurement and feedback system is needed for monitoring these values during treatment to ensure the outcome.

Yu *et al*[82] reported the development of an optical system, combining diffuse reflectance spectroscopy (DRS) for measurement of tumor blood oxygenation and diffuse correlation spectroscopy (DCS) for measurement of tumor blood flow and its application in real time clinical monitoring during interstitial prostate PDT, which was tested on three patients. Prostrate blood oxygen saturation (StO2) was found to decrease only slightly (approximately 3%) after treatment. Prostate blood flow and total hemoglobin concentration over the course of PDT decreased by 50% and 15%, respectively. Johansson *et al*[23] developed an instrument for interstitial PDT on prostate tissue that combines therapeutic light delivery and monitoring of light transmission. They demonstrated this using a system to obtain data on the light distribution within the target tissue and to provide real time treatment feedback based on a light dose threshold model for PDT.

Fluorescence spectroscopy was used by Zaak *et al*[83] to study the feasibility of 5-aminolevulinic-acid (5-ALA)-induced photodynamic diagnosis (PDD) for margin evaluation during radical prostatectomy (RP) in patients with prostate cancer. Eight out of ten patients demonstrated negative margins and one positive margin in fluorescence measurements, which were confirmed by histology. One positive margin in fluorescence measurements was not confirmed.

A few review articles may help interested readers to learn more about optical spectroscopy in prostate cancer management. Hanchanale *et al*[84] reviewed the use of Raman spectroscopy in urological applications including margin assessment during prostatectomy. Manyak *et al*[85] reviewed the advance of medical imaging for prostate cancer including optical techniques such as hyperspectral spectroscopy.

Skin

Because of easy accessibility, skin cancer has been extensively studied in the past two decades both *ex vivo* and *in vivo*. The papers reviewed next were all *in vivo* studies to highlight the most recent progress. Zonios *et al*[86] developed a method for estimating the absorption spectra of melanin *in vivo* based on diffuse reflectance spectroscopy of human skin. They found that the histologic transition from dysplastic nevi to melanoma *in situ* and then to malignant melanoma was reflected in the melanin absorption spectra.

Marchesini *et al*[87] attempted to determine the role of melanin in the various steps of progression of melanocytic neoplasia using diffuse reflectance spectroscopy. They examined 288 melanomas in different phases of progression, i.e. *in situ*, horizontal and vertical growth phase invasive melanomas, 424 dysplastic nevi, and 957 melanocytic lesions. The absorbance spectra in the different groups showed that melanin level was correlated with the progression from dysplastic nevi to vertical growth phase melanomas. In addition, it was observed that *in vivo* diffuse reflectance spectroscopy can be used to differentiate eumelanin and pheomelanin in lesions.

Sterenborg *et al*[88] examined the feasibility of using *in vivo* autofluorescence at an excitation wavelength of 375 nm for the diagnosis of skin cancer in 1995. They did not observe any significant differences in the shape of fluorescence spectra or spatial distribution of fluorescence intensity between tumors and the corresponding control sites, which was likely due to the choice of the excitation wavelength.

As technology has advanced since then, several groups have reported the effective diagnosis of skin cancer using fluorescence spectroscopy. Brancaleon *et al*[89] examined the autofluorescence of normal skin and nonmelanoma skin cancers (NMSC) *in vivo* excited by UV light in 18 patients. They observed that the endogenous fluorescence due to tryptophan residues in both basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) was stronger than in normal tissue, probably due to epidermal thickening and/or hyperproliferation. In contrast, the fluorescence intensity associated with dermal collagen crosslinks was generally lower in tumors than in the surrounding normal tissue, probably because of degradation or erosion of the connective tissue due to enzymes released by the tumor.

Panjehpour *et al*[90] used laser-induced fluorescence spectroscopy at the visible excitation wavelength of 410 nm to detect NMSC *in vivo*. Two hundred and seventy nine measurements were performed in 49 patients. Patients were classified as having either skin types Ⅰ, Ⅱ, or Ⅲ. Cancers were classified correctly in 93%, 89%, and 78% of patients with skin types Ⅰ, Ⅱ, and Ⅲ, respectively. Normal tissues were classified correctly in 93%, 88%, and 50% of patients with skin types Ⅰ, Ⅱ, and Ⅲ, respectively. Using the same threshold, pre-cancerous spectra were classified correctly in 78% and 100% of patients with skin types Ⅰ and Ⅲ, respectively. Benign lesions were classified correctly in 100%, 46%, and 27% of patients with skin types Ⅰ, Ⅱ, and Ⅲ, respectively.

In contrast to UV or visible excitation in conventional fluorescence spectroscopy, Han *et al*[91] developed an NIR autofluorescence and reflectance imaging system excited at 785 nm aiming to characterize cutaneous melanins *in vivo*. Their preliminary results show that cutane-

ous melanin in pigmented skin disorders emits higher NIR autofluorescence than surrounding normal tissue. Because NIR light penetrates deeper in the skin, this technique is expected to examine a larger volume of the skin tissue, which may be useful for clinical evaluation and diagnosis of pigmented skin lesions.

Raman spectroscopy also appears to be an effective optical technique for skin cancer diagnosis. Lieber *et al*[92] used a portable confocal Raman system to measure Raman spectra from 21 suspected NMSC in 19 patients. A 100% (21/21) sensitivity and 91% (19/21) specificity for abnormality, with a 95% (40/42) overall classification accuracy were achieved.

Zhao *et al*[93] reported the development of a rapid real-time Raman spectrometer system with measurement times of less than 1 s in a preliminary study. In total, 289 skin cancers and benign skin lesions were measured. Skin cancers could be well differentiated from benign skin lesions (sensitivity 91% and specificity 75%) and malignant melanoma from benign pigmented lesions (sensitivity 97% and specificity 78%).

For a review on the application of Raman spectroscopy in skin cancer, please refer to Eikje *et al*[94], which includes a survey of introduced sampling methods for IR and Raman spectroscopy in dermatology, and describes the differences between microscopic, macroscopic and fiber-optic measurements of skin cancer. The authors are optimistic about the potential role of vibrational spectroscopy including Raman spectroscopy as a rapid screening tool in dermatology. Krafft *et al*[95] also reviewed the application of Raman spectroscopy in the recognition of a variety of diseases including skin tumors. Mogensen *et al*[96] reviewed the diagnostic accuracy of nonmelanoma skin cancer diagnostic tests and technologies including optical spectroscopy techniques such as spectroscopy and fluorescence imaging. They pointed out the need for larger scale trials despite the promising diagnostic accuracy using optical techniques.

PRACTICAL CONSIDERATIONS OF APPLYING OPTICAL SPECTROSCOPY IN CLINICAL SETTINGS AND COMMERCIALLY AVAILABLE CLINICAL EQUIPMENT

Limiting factors

Multiple factors can affect the feasibility and acceptance of applying optical spectroscopy techniques in clinical oncology. The following factors are particularly important from the author's point of view.

Speed of data acquisition and analysis: Ideally real time data acquisition and analysis is desired. The time of data acquisition depends on the amount of required data and the signal-to-noise ratio. In diffuse reflectance spectroscopy and fluorescence spectroscopy, the signal-to-noise ratio is typically not an issue, thus, real time or nearly real time measurements could be readily achieved[97,98]. Real time *in vivo* measurements in Raman spectroscopy have been achieved in the skin first[99,100], and recently in the endoscopic setting[101] enabled by the advances in ultra sensitive detectors.

Cost of equipment and maintenance: The equipment for *in vivo* diffuse reflectance spectroscopy is relatively cheap because of the advances in white light sources and compact spectrometers. Fluorescence spectroscopy used to require a large investment in relation to its equipment due to the fact that it needs a strong laser in the UV or visible range to excite fluorescence. This cost has decreased quite significantly due to the emergence of new narrow band light sources such as LEDsβ. However, if a range of excitation wavelengths and high sensitivity are needed, a traditional fluorescence spectrophotometer, which uses monochromators for wavelength selection, would still possess advantages, for which the size and cost could go up quickly. The cost of a Raman system is in general the most expensive of these three techniques because of the strict requirement on the wavelength purity of the excitation light and on the sensitivity of the detection module. The required maintenance of systems is minimal in all three techniques, although the calibrations of wavelength accuracy and system throughput should be performed regularly to ensure the accuracy of measured spectra.

Complexity of operation: The equipment operation is straightforward in those commercial systems for all three techniques. Currently, most data analysis algorithms employ multivariate statistical methods to yield a yes/no answer on whether a given sample contains cancer at a certain stage. This information could reinforce the result of the corresponding standard clinical procedure when they agree with each other or remind physicians to double check the sample when they disagree.

Accuracy: Although most studies in the optical diagnosis of cancer have reported high accuracy, there is a large variation in the exact values of accuracy even for the same type of cancer. The potential contributing factors to this situation include differences in the equipment, laser and detector configuration, data analysis algorithms and measurement protocols in addition to inherent inter-patient variation. For this reason, it is necessary for the scientific community to standardize the measurement protocols and other controllable factors that may affect diagnostic accuracy, which would help yield consistent results in the diagnostic accuracy of optical techniques. Such consensus should greatly facilitate the acceptance of optical spectroscopy techniques by the medical community.

Clinical value added to the current clinical procedure: It is imperative to convince physicians that optical spectroscopy techniques can add extra value to clinical cancer management for them to accept the techniques. This would require comparative clinical studies that directly compare the clinical performance of standard procedures and that of revised procedures in which optical spec-

troscopy techniques are incorporated. Such studies will provide the evidence to demonstrate the clinical value of optical spectroscopy added to standard procedures.

Commercially available equipment for clinical applications of optical spectroscopy

Several clinically approved commercial instruments based on optical spectroscopy are available on the market. A few examples are listed below. Tissue oximeters are commercially available and can measure tissue oxygenation in a tissue volume, which is essentially the average contribution of all capillaries and small blood vessels in the tissue volume right underneath the sensor. Most tissue oximeters employ diffuse reflectance spectroscopy[102,103]. Tissue measurements are feasible only when the suspicious site is easy to access. It should be noted that a tissue oximeter is different from a pulse oximeter in that the former measures tissue oxygenation in a local tissue region while the latter measures arterial oxygen saturation. Tissue oxygenation is an important parameter for the diagnosis of many type of cancers.

Fluorescence spectroscopy and diffuse reflectance spectroscopy have been incorporated into a videoendoscopy system to enhance imaging contrast in gastric cancer[104], in which the number of available spectral bands are much smaller than those in point spectroscopy measurements due to the physical restraints in an endoscope. The disadvantage of a small number of spectral bands can be overcome to some extent by a spectral imaging color enhancement technique[105]. In this technique, more spectral bands are reconstructed using a specialized estimation algorithm from the data measured in three spectral bands available in ordinary endoscopy systems. This technique demonstrated certain advantages under several special situations for image enhancement to help visualize Barrett's esophagus.

A commercial cervical imaging system[106] incorporating both reflectance and fluorescence spectroscopy was approved by the US Food and Drug Administration (FDA) in March 2006. This system can be used as an adjunct tool to improve colposcopic detection of high-grade cervical intraepithelial neoplasia (CIN). In two prospective randomized clinical trials, the addition of this system to colposcopy resulted in a 25% or greater increase in the true positive biopsy rate for patients with atypical squamous cell or low-grade squamous intraepithelial lesions on Pap smear, and only a 4% increase in the false-positive rate, compared to those with colposcopy alone.

TECHNICAL CHALLENGES AND STANDARD ISSUES

Technical challenges

Challenges in consistent optical coupling, speed and data interpretation: Optical measurements are quite sensitive to optical coupling, which could cause inconsistent performance of optical techniques. Several strategies can be used to overcome this problem. For example, a pressure gauge could be used to monitor the pressure of probe-tissue contact. Although it works, this strategy requires extra effort from users and additional cost for an automated feedback mechanism. Alternatively, the shape rather than the absolute intensity of the spectra can be used for diagnosis, which would eliminate the problem of optical coupling at the cost of discarding the diagnostic information that may exist in absolute intensity measurements.

Speed is one significant hurdle that prevents the broad use of those optical techniques requiring a large amount of data. While data acquisition speed can be improved by advances in light sources and detectors, a more effective strategy is to acquire and analyze data at only a few optimal spectral bands rather than the entire spectrum. It turns out that this is possible for the determination of specific biomarkers[107]. For this purpose it is important to understand the mechanism of cancer development because it would help identify most diagnostic biomarkers and find corresponding optimal spectral bands.

Data interpretation is another important issue that deserves significant attention. Currently, most data analysis algorithms in optical spectroscopy yield a definite "yes/no" result for a given tissue sample. This may not be the best solution in an *in vivo* scenario because it excludes the possibility of an intermediate status and could result in artificial errors. A better choice might be to calculate the probability for a given tissue sample to be a cancer. This probability could be determined for all pixels in a small area, in which the spatial context would help clinicians determine the true answer.

Translation to spectral imaging and microscopic imaging: It seems natural for optical spectroscopy to evolve from point measurements to spectral imaging to cover a large field of view. Images also provide a spatial context similar to what physicians typically see in clinical settings. Because of time restraint, spectral imaging often contains much fewer spectral bands, thus, could be less sensitive to malignant changes in tissues compared to the entire spectrum. Therefore, a combination of spectral imaging and point measurements might be most useful, in which spectral imaging data help locate suspicious areas, while point spectroscopy measurements can check identified sites in detail. This approach has been demonstrated to be effective in an endoscopic setup[60]. The challenges in handling a large amount of data, speeding up data acquisition and accommodating complex illumination-collection configurations need to be addressed before spectral imaging could be useful in clinical settings.

Optical spectroscopy using a fiber-optic probe examines a large tissue volume, which could result in low sensitivity in a small target such as a small tumor. This can be serious in Raman spectroscopy, because Raman signals are typically low in tissue samples. Microscopic imaging at a high spatial resolution[108] in an endoscopic setup has been demonstrated, which can overcome the above problem. In the laser scanning mode, excitation light can be focused on a small spot to enhance the sensitivity to the target area and increase emission signals.

Quantitative optical spectroscopy and imaging: Opti-

cal spectroscopy can be used to quantify several biochemical and biophysical parameters in tissues as discussed in this review. Light transport models such as diffusion theory or the Monte Carlo method were used to relate tissue optical properties to optical measurements. Moreover, physical laws such as Beer-Lambert's law and Mie approximation were used to link biochemical and biophysical parameters to tissue optical properties. The resulting parameters, such as hemoglobin concentration and oxygenation, the average size of scatterers *etc*, could be correlated with the physiology of tissues, which provides insight into cancer development. These parameters could also be used for cancer diagnosis, which provides an alternative to pure statistical classification.

Although this approach has achieved great success, several assumptions made in this approach impose limitations on the interpretation of results and its applications. For example, most such models assume a semi-infinite homogeneous tissue model, in which the concentrations of chromophores are distributed uniformly. The Mie approximation assumes perfectly spherical scatterers. Although the models with these assumptions have yielded meaningful results, they definitely do not fully exploit all the diagnostic information present in optical spectroscopy. Several attempts[109,110] have been made to build more realistic tissue models, for example, applying a layered tissue model instead of a homogeneous tissue model or inhomogeneous scattering particles, to further refine the techniques.

Standard issues

Establishment of standards for the evaluation of techniques: It is important to establish standard methods to evaluate new optical techniques in order to be compatible with those established imaging techniques and be accepted by clinical practitioners. Currently each optical technique is evaluated by the group in which it is developed using a somehow unique method. For optical techniques targeting a similar clinical application, it might be helpful for leading groups to establish recommended standards in the protocol of evaluation, for instance, the size of the patient population and distribution of age and gender, the table or plots that demonstrates representative results and the measures of accuracy *etc*. These standards will facilitate the comparison across different techniques from the point of view of clinicians as well as colleagues in the scientific community. Although such principles may have existed in the phase of clinical research, the author believes that it is worth setting up similar standards even at the early stage of technical development for the purpose of evaluation. These are similar to those industrial standards and aim to maintain high quality and good reliability of scientific research, which will help the technique get accepted by the medical community at a later stage.

Compatibility of optical techniques with current procedures: It is quite clear for some optical techniques that they cannot fulfill the requirement of assumed tasks alone. The unique advantage of high optical contrast makes optical techniques complementary to most existing imaging modalities. Once the capability of an optical technique is well understood, it would be helpful to perform clinical studies to decide how the optical technique could fit into the current procedure in cancer management. Since the current procedure typically contains the use of those established techniques, it would be more acceptable if the optical technique could be integrated into the established technique and provide extra valuable information without incurring unjustifiable cost and time commitment. Some pioneering efforts[16,38,111] have been made to investigate the complementary attributes of optical spectroscopy and MRI in breast cancer management.

CONCLUSION

Because of its non-invasiveness and high optical contrast, optical spectroscopy has been intensively studied in cancer diagnosis and has demonstrated great potential in finding its unique role in clinical cancer management. Some commercial instruments based on optical spectroscopy have been approved for clinical use. It is reasonable to anticipate that more optical spectroscopy techniques will find their niches in clinical settings given the dramatic increase in the market and research in the field of biomedical optics. Achieving this goal would require the collaborative efforts of both the scientific community and the medical community worldwide.

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