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ABSTRACT

Terahertz radiation has significant potential in medical diagnosis and treatment because its frequency range corresponds to the characteristic energy of biomolecular motion. Advantageously, terahertz-specific low energy does not cause the ionization of biomolecules. In this paper, we review several state-of-the-art terahertz biomedical techniques and results and suggest potential techniques that may be applicable in real-world clinics in the near future. First, some techniques for enhancing the penetration depth into wet biological tissues are surveyed. Endoscopy and otoscopy methods for approaching internal organs are then discussed. The operation principles of sensors utilizing terahertz radiation are explained, and certain sensing examples related to blood disorders, diabetes, and breathing conditions are presented. The greatest potential of terahertz radiation in biomedical applications so far has been in cancer imaging, because terahertz radiation is ideal for measuring the superficial soft tissues in which most cancers occur. The examples presented herein include skin, oral, gastric, breast, and brain cancers. In search of a cancer-specific signal using terahertz radiation, methylated malignant DNA has been found to exhibit a characteristic resonance at approximately 1.65 THz. This resonance may help treat cancer through the demethylation of malignant DNA using high-power terahertz irradiation at this specific frequency, as well as serving as a potential cancer biomarker.

I. INTRODUCTION

Since Hu and Nuss first demonstrated terahertz (THz) imaging with a wet leaf drying over time,[1] researchers have realized the potential of THz radiation for biological and medical applications. Owing to its low energy in the millielectronvolt range, THz radiation does not ionize molecules, presenting a significant advantage in medical imaging over X-rays, which can cause biological molecules to break down. More importantly, the THz energy spectrum covers the characteristic energies of biomolecular collective motions such as vibration, rotation, and libration, as well as the low energy of hydrogen bonds which are abundant in water-based biomedical samples. Specifically, this implies that THz radiation is an excellent radiation source for biological and medical studies, exhibiting high sensitivity in measurements targeting changes in biomolecules, cells, and tissues. Exploiting these properties, THz radiation has been utilized to study water[2,3] and various biological molecules[4–6] and to image diseased tissues, including tumors.[3,7,8] In this paper, the authors provide perspectives on practical applications of THz radiation that could soon be commercialized and adopted in clinics with the aim of diagnosing and treating diseases.

THz radiation is unable to reach deep into wet biological tissues because it is heavily attenuated by water molecules. For example, it can penetrate only a couple of hundred micrometers into the human skin.[9] Several techniques, however, allow THz radiation to penetrate deeper into wet tissues, including the freezing technique[10] and the penetration enhancing technique using gelling agents.[11] These methods are discussed with specific examples. For the imaging and sensing of the internal organs, endoscopy and otoscopy methods are also discussed.

THz sensors combined with state-of-the-art metamaterial technology have been employed to measure an infinitesimal quantity of biological molecules, helping to diagnose diabetes or blood-/breathing-based medical conditions. These sensors and their modes of application are summarized.

One of the most promising medical applications of THz radiation is cancer imaging. Most cancers start on the surface of soft tissues, which are the ideal target for superficial imaging using THz radiation.[9] Many researchers have investigated the diagnostic imaging of various cancers, including skin, oral, gastric, and brain cancers. In looking for a cancer-specific fingerprint, Cheon *et al.* observed a resonant feature at 1.65 THz associated with various types of cancer.[12] This resonance is believed to originate from methylated DNA and might serve as a universal cancer biomarker.

There is a wealth of evidence showing that the demethylation of malignant DNA helps to recover gene expression, induce cell apoptosis, and reduce the tumor size. These effects are achieved using specific demethylation drugs such as decitabine.[13] Demethylation using the resonant absorption of high-power THz radiation might induce a similar effect, enhancing the efficacy of cancer treatment. The electromagnetic demethylation of malignant DNA is briefly discussed as a potential cancer treatment method.

II. TECHNIQUES FOR CLINICAL APPLICATIONS

A. THz, TDS, and CW systems

The electromagnetic waves constituting THz radiation for biomedical spectroscopy and imaging can be generated and detected in pulsed- or continuous-wave (CW) forms. THz time-domain spectroscopy (TDS), based on ultrafast lasers,[14,15] introduces complex optical constants in the form of the refractive index and absorption constant[16] of the specimen, representing the time delay and amplitude reduction, respectively, of THz electromagnetic pulses induced by molecular interactions with the material under study. The consequent time-domain pulses facilitate time-of-flight imaging because they are coherently measured.[17–19] General THz-TDS systems based on a 800-nm Ti:sapphire oscillator or a 1.5-μm telecommunication fiber laser supply microwatt-level average powers of up to several THz in frequency. The high-field THz pulses generated using air plasma[20] or tilted nonlinear optical crystals[21] driven by a regenerative laser amplifier can be used to investigate high-field THz effects on biological molecules, cells, and tissues with milliwatt-level average powers.[22] In contrast, CW THz sources and detectors can be miniaturized at a lower price, as the system can be built without an ultrafast laser. Such sources have been developed using photomixing technology with optoelectronic devices,[23] high-speed transistors,[24,25] resonant tunneling diodes,[26] quantum cascade lasers (QCLs),[27] backward wave oscillators,[28] Schottky diodes,[29] and gyrotrons.[30] The single-frequency radiation from the above sources is detected using bolometers,[31] pyroelectric detectors,[32] Schottky diodes,[33] and other optoelectronic detectors.[34]

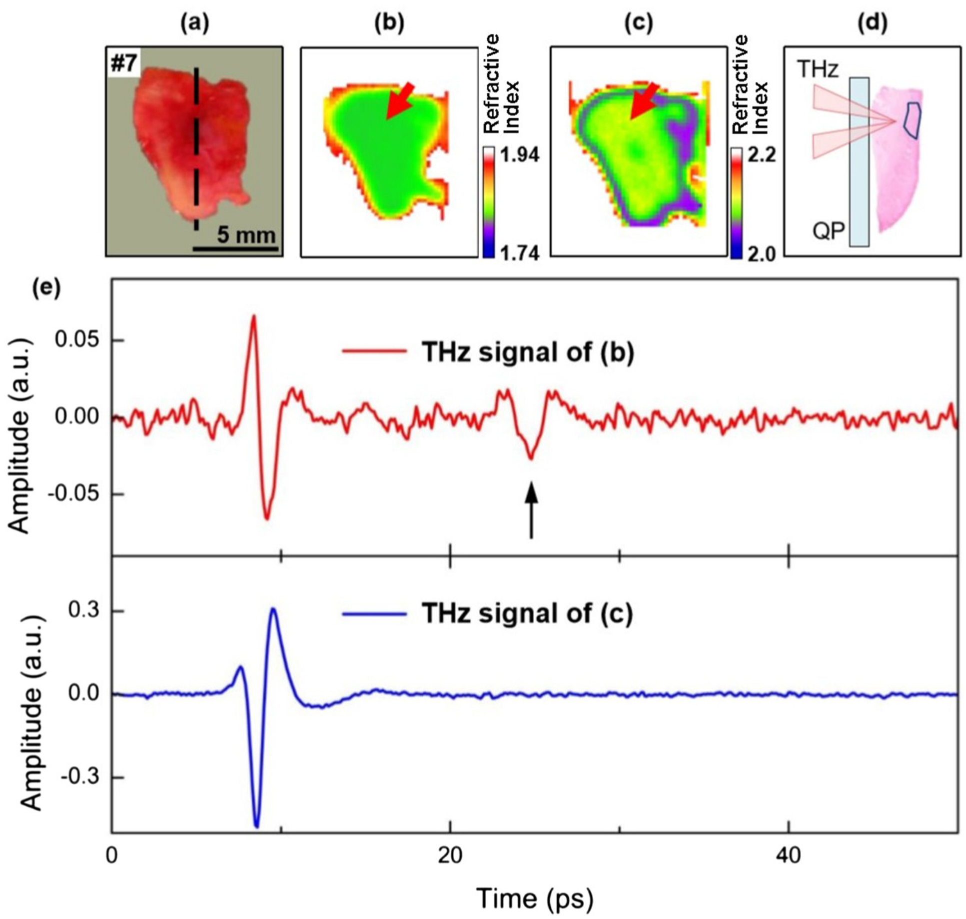

FIG. 1. An oral malignant tumor inside a frozen sample detected by observation of the THz time-domain waveform. (a) Visible image, and THz images at (b) frozen and (c) room temperature. (d) An experimental scheme and pathological image of the tissue sample in a perpendicular section (THz: THz radiation and QP: quartz plate). (e) THz waveforms of the red arrow regions in the tumor at the frozen temperature of (b) and room temperature of (c). The second pulse (black arrow) presented in the THz waveform of (b) was caused by reflection from a tumor inside the sample. This result indicates that the penetration depth of THz radiation increased enough to reach the tumor lesion at 1.3 mm from the surface. Reprinted with permission from Sim *et al.*, Biomed. Opt. Express **4**, 1413 (2013). Copyright 2013 Optical Society of America.

Regardless of the type of source and detector, the image acquisition speed is one of the most critical challenges when using THz radiation for medical imaging. The imaging speed using a point source and detector is slow because the sample must be scanned in a point-by-point manner. Although the two-dimensional Galvano scanner and fast detector or the signal processing techniques[35–37] improve the scanning speed, a large field of view is required for real-time imaging.[38] The development of an uncooled bolometer array and THz QCL enables real-time THz imaging,[39] which is a good example of the direction that THz medical imaging systems should take. Another problem with THz medical applications is the low penetration depth, as the high absorption of THz radiation by liquid water means that depths of only a few hundred micrometers can be penetrated in wet samples such as human tissue. This physical limitation of screening by water molecules also makes it difficult to reach internal body organs.

B. Frozen THz imaging

THz radiation cannot penetrate deep into wet biomedical tissues because the radiation absorbance of water molecules is greater than 200 cm^{-1} at 1 THz and room temperature. For instance, the penetration depth of THz radiation in human skin is limited to a couple of hundred micrometers.[9,40] Several groups have proposed freezing techniques to increase the penetration depth of THz radiation into wet tissues,[41–44] as the absorption coefficient of ice is one order of magnitude lower than that of liquid water.[9] Therefore, THz radiation can penetrate deeper when the tissue's water molecules are frozen. As shown in Fig. 1, Sim *et al.* observed a second pulse reflected from a tumor situated at a depth of 1.3 mm in frozen oral tissue; this depth could not be reached without freezing.[10] They were also able to differentiate between the malignant and benign regions of tissue, which are difficult to distinguish under fresh conditions, using the freezing technique. The freezing technique enables observation of the structural states of cells and chemical information of molecules in tissue, as the background effect induced by the water molecules is suppressed. The same group detected lymphatic metastases that were difficult to distinguish in the fresh state by freezing the lymph node.[42] Png and co-workers adopted the freezing technique to characterize brain tissue samples altered by Alzheimer's disease.[43] Recently, Cheon *et al.* reported that the THz resonance of methylated DNA from solid cancer cell lines, otherwise difficult to observe in aqueous solution, could be measured using the freezing technique.[12] This will be explained in more detail in Sec. III.

C. Penetration-enhancing agents

The freezing technique has certain limitations in clinical use, as the freezing process might occasionally cause tissue necrosis. To overcome these limitations, Oh *et al.* proposed a penetration-enhancing agent (PEA) to increase the THz radiation delivery depth into fresh wet tissue. They used glycerol as the PEA material, which is biocompatible and is a common ingredient in cosmetics and food. Glycerol is easily absorbed by the human skin and tissue, whereas its radiation absorption coefficient is much lower than that of water in the THz frequency range. As shown in Fig. 2, when glycerol was applied to the skin of a mouse, the THz radiation penetrated further and the THz image acquired under the skin, which is reconstructed by the second pulse reflected from the metal blade below the back of the skin, was noticeably clearer.[11] Kim *et al.* investigated the dynamics of drug delivery through the skin barrier. They considered the delivery process of dimethyl sulfoxide (DMSO), used as an optical clearing agent for visible light, into mouse skin, and subsequently compared the results with those obtained through conventional invasive measurement methods such as the Franz cell diffusion test. Their study demonstrated that THz radiation is useful for the noninvasive assessment of in-skin drug delivery.[45,46]

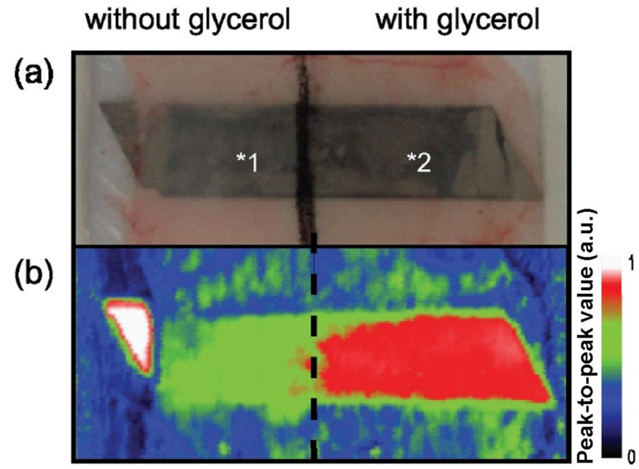

FIG. 2. Enhancement of the penetration depth of THz radiation using glycerol as a penetration-enhancing agent. The size of the images is 5×3 cm^2. (a) Visible image of a metal target below the abdominal tissue of a mouse. (b) The tissue on the right side was treated with glycerol, which has lower absorption and phase delay under THz radiation. The treatment resulted in higher contrast in the THz imaging. Reprinted with permission from Oh *et al.*, Opt. Express **21**, 21299 (2013). Copyright 2013 Optical Society of America.

D. Endoscopy and otoscopy

Tumors under the skin or mucosa can be detected using penetration depth enhancing techniques such as PEAs or freezing. However, lesions of internal organs such as the oral cavity, digestive organs, respiratory organs, and the middle ear can only be approached using THz endoscopes such as a laparoscope, tracheoscope, and otoscope. Ji *et al.* fabricated a small THz endoscope, housing both the generator and the detector in a package size of 4×4 mm^2 in cross section and 6 mm in length, based on a pair of photoconductive antennas. They then measured the complex THz optical coefficients of the tissue in the human oral cavity using this small handheld THz-TDS module.[47] The group also developed a THz otoscope that enables the detection of otitis media, as shown in Fig. 3. Otitis media is a disease that causes fluid and purulence in the posterior part of the tympanic membrane within the middle ear. Their THz otoscope measures the change in water content on the tympanic membrane due to tissue hydration and

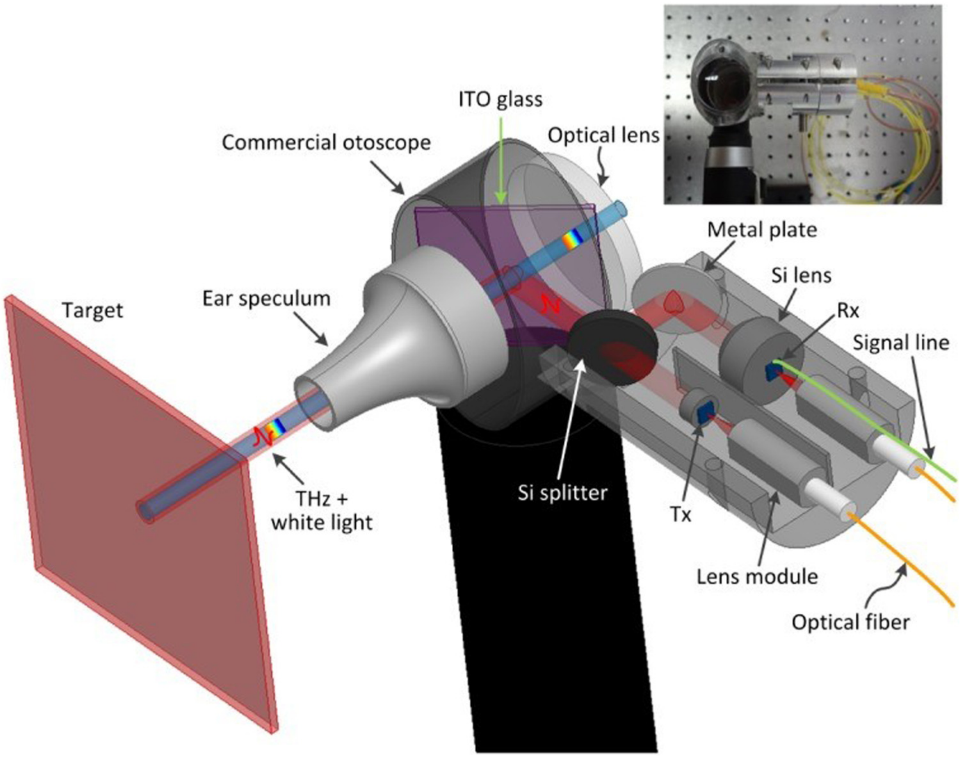

FIG. 3. Schematic diagram and photo of a practical THz otoscope. The otoscope is an integrated device composed of a clinical optical otoscope and fiber-coupled THz module, which is a representative example of practical THz medical equipment for diagnosing diseases. Reprinted with permission from Ji *et al.*, Biomed. Opt. Express **7**(4), 1201 (2016). Copyright 2016 Optical Society of America.

is, therefore, applicable as a medical device for otitis media diagnosis.[48,49] THz waveguides can also be applied for THz endoscopy, with Awad *et al.* obtaining a THz near-field image using a tapered Sommerfeld wire waveguide.[50]

E. Sensors and microfluidics

Besides imaging for the *in vivo* detection of diseases, THz devices and systems can facilitate the development of *in vitro* diagnostic medical devices (IVDs), enabling early disease detection from sample specimens such as blood, body fluid, or breath. THz IVDs should be able to differentiate tiny amounts of specimen rapidly, such as nucleic acids, proteins, or various metabolites, at the molecular level. For example, George *et al.* reported a THz microfluidic device that, from a small sample of 10 pmol, measures the absorbance spectrum of bovine serum albumin in the frequency range 0.5–2.5 THz.[51] Serita *et al.* developed a nonlinear optical crystal-based THz microfluidic chip with several arrays of split ring resonators (SRRs) and measured the ion concentration of 31.8 fmol in a 318 pl aqueous solution[52] (Fig. 4).

III. *IN VITRO* SENSING

Nanostructures such as SRRs and nanoantennas enhance the THz response at a specific resonance frequency, enabling highly sensitive detection of biochemical molecules and materials. Lee *et al.* selectively measured a tiny amount of pesticide (8 ppm) using a nanoantenna metamaterial sensor.[53] The same group also

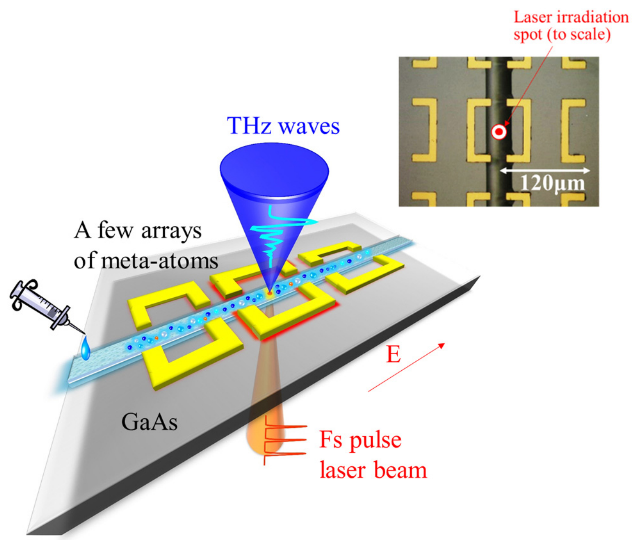

FIG. 4. A THz microfluidic chip based on a nonlinear optical crystal (GaAs) with split ring resonators (SRRs) through which the liquid solution flows. An optical microscope image of SRRs and the microfluidic channel in a fabricated chip (upper right). The THz chip can be used to measure a small quantity of materials in body fluids for pathological examination as an *in vitro* diagnostic medical device (IVD). Reprinted with permission from Serita *et al.* APL Photonics **3**(5), 051603. Copyright 2018 AIP Publishing LLC.

improved the sensitivity of the metamaterial sensor by combining it with graphene, enabling them to detect single-stranded DNA by type.[54] Nanomaterials such as nanorods and nanoparticles have been employed in the selective measurement of biomedical materials by increasing the specificity of targeted biological events. Oh *et al.* demonstrated molecular imaging with THz radiation that selectively identified the tumor at the molecular level using target-specific antibody-treated nanoprobes.[55–58] They obtained *in vivo* THz images of the A431 tumor (epidermoid carcinoma) using gold nanorods specially designed for targeting the epidermal growth factor receptor (EGFR), which is overexpressed by carcinogenesis.[55] Instead of relying on sensing based on labels such as nanoprobes, THz radiation detects biochemical changes with higher specificity because many collective vibrational motions of biomolecules exhibit resonance in the THz range. Without using labeling agents, Cheon *et al.* directly measured the resonance of the methyl-DNA bond at a frequency of 1.65 THz, which is caused by a chemical change during the malignant process, as shown in Fig. 5.[12] This study highlighted the possibility of developing a cancer treatment using THz radiation at the DNA level; this is discussed in further detail in Sec. V. The methyl-DNA resonance could be more sensitively detected for the *in vitro* diagnosis of cancer if metamaterial sensors were operated at the resonance frequency. The development of such highly sensitive THz sensors would enable the construction of novel IVDs that are capable of diagnosing cancer, diabetes, and other diseases by measuring changes in gene information, chemical composition, or blood sugar level.

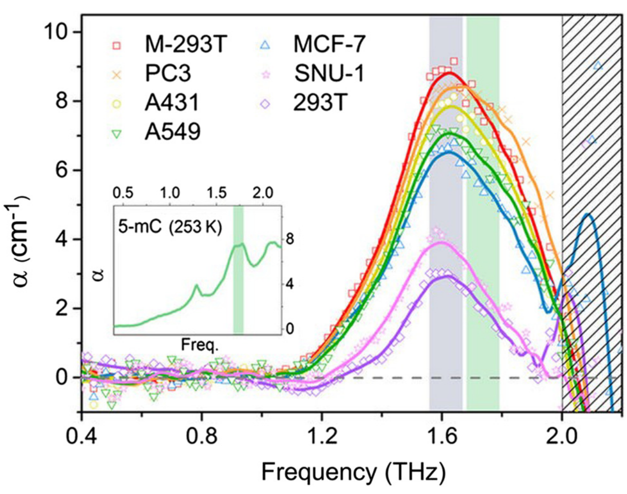

FIG. 5. THz resonance peaks of the methyl-DNA bond in normal DNA (293T DNA), artificially methylated DNA (M-293T), and cancer DNAs (PC3, a prostate cancer cell line; A431, an epidermoid carcinoma cell line; A549, an adenocarcinomic lung cell line; MCF-7, a breast cancer cell line; and SNU-1, a gastric carcinoma cell line) within aqueous solution. The amplitudes of the resonance peaks are dependent on the cancer type. The resonance peak of DNA could serve as a cancer biomarker to realize early detection. The inset spectrum shows the resonance peaks of 5-methylcytidine (5-mC). Reprinted with permission from Cheon *et al.*, Sci. Rep. **6**, 37103 (2016). Copyright 2016 Springer Nature.

THz IVDs have strong potential in the early detection of many diseases using extracted specimens such as body fluids or breath. Several groups have reported the specific diseases to which THz techniques could be effectively applied. The sensitivity of THz radiation to water and biomolecules allows changes in the components of body fluids to be measured, such as blood, lymph, and urine in the body. The characterization of body fluids assists the diagnosis of various diseases, including diabetes and blood cancer. Jeong *et al.* measured the THz optical constants of blood, plasma, and red blood cells (RBCs). They showed that the RBC concentration could be quantified using THz radiation, which is useful for diagnosing diseases related to the quantity of RBCs, such as anemia and dengue fever.[59] Chen *et al.* observed a linear relationship between the blood glucose level and THz absorbance in 70 diabetic patients, which demonstrates that THz blood analysis techniques could help to detect diabetes. The correlation between the measured THz absorption and glucometer values had an error rate lower than 15% in 20 blood samples.[60] Using a nanoslit antenna, Lee *et al.* sensed a sugar concentration of a few hundred micromoles.[61] Gases originating from exhalation and flatus could provide information for diagnosing bronchial asthma and lung or colon cancers. THz spectroscopy could be employed as a high-sensitivity gas sensor owing to the correspondence of various gas molecules' rotational energy to specific THz frequencies. Fosnight *et al.* measured ethanol, methanol, and acetone gases at femtomole concentrations, demonstrating that THz radiation can be applied to the diagnosis of respiratory diseases by analyzing the molecular components of exhalation in patients with asthma or pemphigus.[62] Gas spectroscopy for volatile organic compounds in human breath was also conducted with SiGe BiCMOS circuits, which would realize a practical system at a reasonable cost.[63]

IV. CANCER IMAGING

Along with *in vitro* sensing, THz radiation has been applied to the imaging of cancer tissues. An early cancer diagnosis increases the survival rate and reduces the risks of complex surgery associated with more advanced-stage cancer treatments. Determining an accurate boundary between cancerous and normal tissues and invasion depth information for a cancer lesion at the initial stage may also prevent cancer recurrence. In the early stages, THz radiation methods provide more accurate detection of the malignant tissue's boundary and invasion depth than conventional imaging modalities such as computed tomography (CT), magnetic resonance (MR), and ultrasound imaging. This is because most solid cancers start on the surface of soft tissues, and conventional techniques are not optimal for imaging superficial soft tissues.[9] THz radiation is also sensitive to the changes in hydration level and cellular structure that arise in the malignant process. In this section, we discuss THz imaging results for skin, oral, breast, and brain cancers reported by several research groups.

A. Skin cancer

Skin cancer is one of the most common cancers in Western Europe. It is very important to determine the exact boundary of the malignant tissue for accurate resection, as this helps to prevent recurrence. However, the precise boundary below the surface of the skin cannot be detected by visual imaging or MR imaging which has poor performance up to several millimeters below the surface.[9]

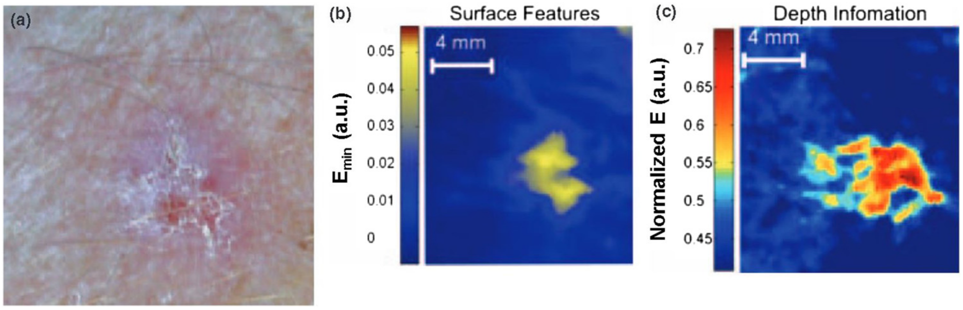

FIG. 6. *In vivo* THz images of a nodular basal cell carcinoma (BCC, skin cancer) on the arm of a patient. (a) Photograph of the cancer lesion. (b) THz image of (a) from the minimal value of the THz waveform. The image shows the surface of the lesion. (c) THz image of the tumor at 250-μm depth. THz diagnostic imaging provides accurate information on skin cancer. Reprinted with permission from Wallace *et al.*, Br. J. Dermatol. **151**, 424 (2004). Copyright 2004 John Wiley & Sons, Inc.

Wallace and co-workers reported THz imaging of skin cancer tissues *ex vivo* and *in vivo*.[64–66] As shown in Fig. 6, the general clinical image does not accurately identify the cancer distribution under the skin surface. However, the THz images clearly display not only the cancer distribution on the skin, but also the extent of the cancer invasion into the skin, which in this case was 250 μm in depth.[66] Such accurate depth and boundary information enables the surgeon to excise only the malignant region and minimize the unnecessary removal of normal tissue. These advantages of THz imaging in epithelial tissues indicate strong potential for cancer detection on the surfaces of internal organs, enhancing diagnostic capability in cases such as oral and digestive cancers.

B. Oral cancer

Oral cancer is a type of epithelium carcinoma that is similar to skin cancer. The oral area consists of many organs such as the oral cavity, tongue, teeth, etc. Therefore, a precise surgical excision of the tumor requires exact borderline information measured using a compact device such as a THz endoscope rather than bulky MR or ultrasound (US) imaging. Sim *et al.* determined the boundary of oral malignant tissue using the freezing technique. Oral cancers are difficult to distinguish from normal tissue regions owing to the higher water content in oral tissue than in healthy skin. The freezing technique suppresses the background effect of water on the THz radiation, allowing the difference in cellular structures between the normal and malignant regions to be observed. Thus, THz radiation was able to penetrate and locate the cancer deeper inside the tissue, as discussed earlier.[10,44]

C. Digestive cancer

Gastric cancer commonly arises under the surface of an organ, such as mucosa. The cancer invasion depth and distribution information determine the after-treatment prognosis as well as the treatment method, which could be either endoscopic (sub-)mucosa resection or general surgery.[67,68] Visible endoscopes cannot observe cancer in the submucosa and US endoscopes have a limited ability to determine the boundaries of the cancer because of contrast issues. Ji *et al.* reported that THz imaging was able to detect the tumor boundary using early gastric cancer tissues sampled from eight patients.[67] THz imaging was performed on cancer tissues obtained by endoscopic submucosal dissection and compared with pathological mapping reference images (in normal tissue areas) to demonstrate that the THz technique is useful for gastric cancer observation. They also characterized gastrointestinal tissues such as the esophagus, stomach, small intestine, and large intestine of animals using a reflective THz imaging method.[68] The results showed that a gland in the gastrointestinal tract of rats caused different signal intensities in the THz images. This finding suggests that THz radiation is not only able to detect gastric and colon cancers, but could also provide a cancer prognosis by detecting preneoplastic states such as internalization and Barrett's esophagus.

D. Breast cancer

Minimizing surgical excision is much more important for breast tumors than for oral or gastric cancer treatments because of the impact on quality of life and subsequent psychological and functional problems. MR imaging and mammograms based on x-rays have conventionally been used to detect breast tumors. These processes are very uncomfortable for patients and rarely provide information on the exact boundary during breast-conserving surgery.[69] Numerous THz breast cancer imaging results suggest that THz technology can effectively determine the boundary of tumors.[69–72] Fitzgerald *et al.* obtained THz images of 22 breast cancer tissue specimens resected from 22 women and compared the size and shape of the tumor site on the THz images with the histopathologic ones.[69] Grootendorst *et al.* scanned 48 resected breast cancer samples with a handheld THz probe system and compared them with pathological results.[72] They obtained an accuracy, sensitivity, and specificity of 75%, 86%, and 66%, respectively, using a support vector machine learning model and 69%, 87%, and 54%, respectively, using a Gaussian wavelet deconvolution approach (with Bayesian classification).

E. Brain cancer

The brain is a representative high-lipid organ owing to the myelin content around neurons. The lipid content yields a high contrast in THz images of brain cancer, because the tumor contains

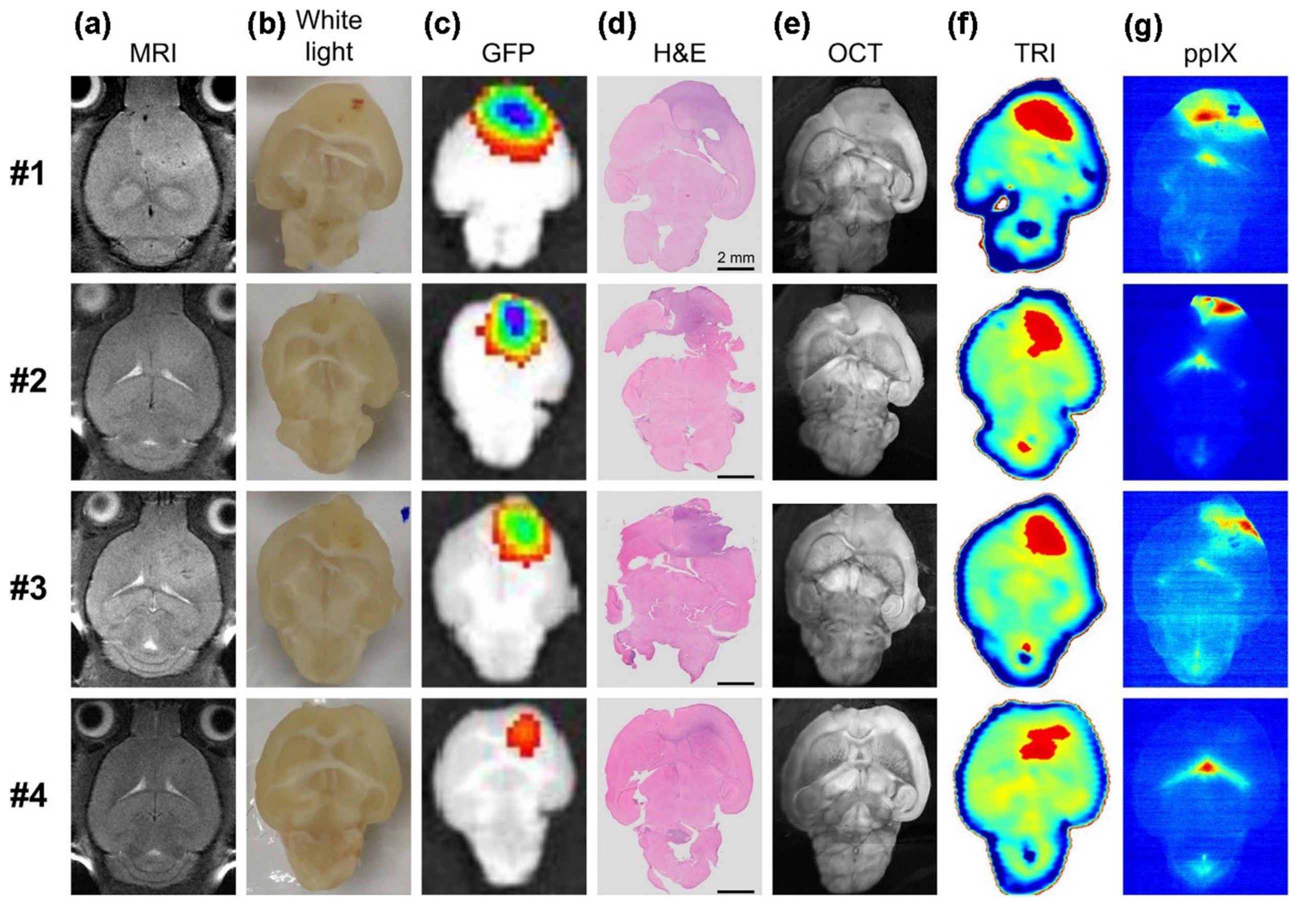

FIG. 7. Comparison of THz reflectometry (TR) with multimodality imaging of enhanced green fluorescent protein (eGFP)-transfected human glioblastoma (GBM) tumor-sphere in tumor-bearing mice. (a) Magnetic resonance (MR) images of the brain for validation of tumor *in vivo*. (b) Visible images (white light) of the excised brain. Identifying the tumor regions in MR and the visible images is difficult. (c) GFP fluorescence images. (d) Image from hematoxylin and eosin (H&E) stain. The two imaging modalities visualize the tumor regions using labeling methods (fluorescence and stain). (e) Optical coherence tomography (OCT) images. OCT shows detailed information of tissue structure but cannot identify the tumor region. (f) TR images with peak-to-peak values of the time-domain waveforms. The tumor regions are clearly displayed with high-intensity red areas in TR images without labeling. The THz results agree well with the true tumor regions of (c) and (d). (g) 5-ALA-induced protoporphyrin IX (ppIX) fluorescence images. ppIX imaging is a real-time clinical method for discriminating the tumor boundary during surgery. TR images of tumor regions show higher accuracy than ppIX fluorescence images. This study demonstrates that THz imaging has the potential to determine the brain cancer boundary accurately without using fluorescent dye. Reprinted with permission from Ji *et al.*, Sci. Rep. **6**, 36040 (2016). Copyright 2016 Springer Nature.

elevated protein concentrations responsible for high THz radiation absorption, whereas lipids are less radiation-absorbing. Because of the functional significance of the brain, precise surgery that saves normal areas while only eliminating the malignant tumor is absolutely necessary. MR, CT, and fluorescence imaging techniques are employed to delimit the cancer boundary. However, the boundary of brain cancers such as glioma is not clearly distinguishable through optical microscopes during surgery. Oh *et al.* demonstrated that THz imaging is able to determine the border of the malignant region using animal brain tumor models.[73] Ji *et al.* also reported that THz imaging could be very helpful in detecting brain tumors using patient-derived cancer models that present the same properties as the diffuse boundary of human brain tumors.[74] They compared the THz images of tumor-bearing brain tissues with data obtained through imaging methods such as visible photographs, hematoxylin and eosin (H&E) staining, optical coherent tomography, and protoporphyrin IX (ppIX) fluorescence imaging. As shown in Fig. 7, THz imaging delimits the tumor areas within all four presented samples, in agreement with the H&E stained images, whereas the other optical imaging techniques do not distinguish the tumor without the use of fluorescent dye.[74] Ji *et al.* also performed *in vivo* THz imaging that clearly displays the tumor region, as shown in Fig. 8.[74] This study strongly suggests that neurosurgeons could use THz imaging technology to determine the tumor margins during brain surgery, once the tumor has been confirmed by MR imaging, because the THz image exhibits high contrast. In this case, fluorescent imaging is inaccurate and inconvenient to patients. A human brain tumor excised by neurosurgeons was subsequently tested in the lab,

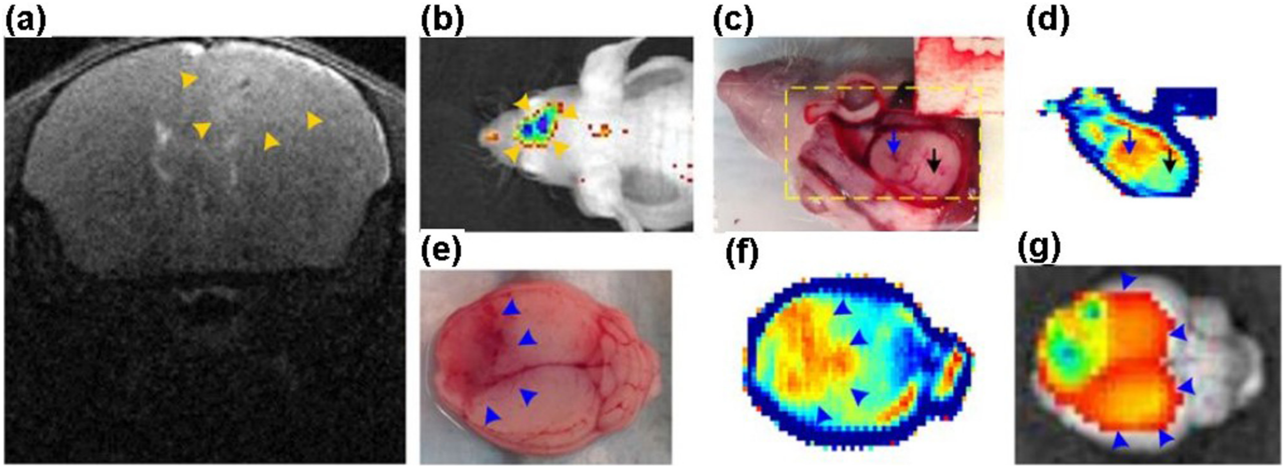

FIG. 8. THz reflectometry (TR) imaging for *in vivo* tumor detection. (a) Magnetic resonance (MR) image of a mouse's brain. (b) Overlap image of green fluorescent protein (GFP) and MR images *in vivo*. The yellow-orange arrow indicates the tumor region. (c) Visible image of the exposed brain. TRI was applied in the yellow-dashed box. (d) TR image of the brain *in vivo*. The tumor region (blue arrow) is well distinguished from the normal region (black arrow). (e)–(g) Extracted whole brain images produced by visible, TR, and GFP imaging methods. TR image agrees well with the actual tumor region in the visible image. However, the GFP image is broader than the actual tumor region because of the diffusion of the fluorescence signal in tissue. Nonlabeled THz brain imaging has higher contrast and accuracy than MR imaging and fluorescent imaging *in vivo*. Reprinted with permission from Ji *et al.* Sci. Rep. **6**, 36040 (2016). Copyright 2016 Springer Nature.

confirming that the brain tumor and normal tissue were well distinguished by THz imaging. Therefore, THz imaging for brain cancer has the potential to use in clinical surgery due to its great ability of boundary distinction.

Although THz radiation is an excellent tool for imaging cancerous tumors that grow from the surface of soft tissues, it is difficult to break into the medical imaging market because current imaging modalities such as MR imaging and x-ray CT are widely utilized, and surgeons and radiologists are heavily dependent on them. As an intermediate step to *in vivo* THz imaging for clinics, THz researchers and engineers can consider *ex vivo* THz imaging for histology as a first commercial product. Surgeons currently judge the accuracy of tumor resection using H&E stained images, but these require at least a couple of days before the results can be observed. Therefore, they sometimes use frozen sectioning to make quick decisions in the operation room, although this technique is not especially reliable.[75] THz radiation could be used with the freezing technique described in Sec. II B to build a "THz histology microscope" for *ex vivo* imaging during surgery. This can be realized at relatively low cost with a reasonable spatial resolution if solid-state sources and detectors are employed, such as high-speed transistors or resonant tunneling diodes. With such a THz histology microscope, we would be able to accumulate a large number of clinical cases that, in turn, would assist the rapid development of *in vivo* THz cancer imaging systems.

For *in vivo* applications, the THz technique would be expected to offer significant merit over MR imaging and X-ray CT as an alternative imaging modality although it is advantageous when imaging superficial soft tissues. Conventional imaging techniques use a simple contrast mechanism to detect the change in signal intensity without taking specific features into account. However, THz cancer imaging might be realized by specific signals originating from cancer or a cancer biomarker in the THz region, as shown in Fig. 5,[12] and this is a substantial benefit over conventional modalities. However, the THz spectroscopic imaging system would have to deliver a very high signal-to-noise ratio of at least 100 dB to measure the resonance signals from human tissues directly while the current THz system, which measures the resonance from extracted DNA, typically uses an 80-dB ratio. Although this presents an enormous technical challenge for THz system developers, it is worthwhile devoting effort to this problem because it gives the opportunity to compete with MR imaging and X-ray CT in the field of cancer imaging.

V. CANCER THERAPY

The THz cancer imaging technique described in Sec. IV utilizes the spatial difference in optical constants to construct the image. The method relies on discriminating the refractive indices or absorption coefficients between the benign and malignant regions of tissue. The difference emerges from the change in water content and cell density induced by the malignant process, but does not include any specific feature such as resonance arising from disease-induced molecular changes. The authors found a resonant feature of DNA from cancer cells at 1.65 THz, as shown in Fig. 5.[12] This resonance is caused by the methyl-DNA bond, as briefly described in Sec. III. DNA methylation is an epigenetic change that occurs regardless of sequencing and induces genetic mutations that could eventually cause cancer.[76] Demethylation improves the outcome of cancer treatment in terms of gene reprogramming, cell apoptosis, and tumor shrinkage.[77–79] Moreover, the efficacy of cancer treatment during chemotherapy significantly increases when demethylation is enhanced by an antineoplastic chemical drug called decitabine.[13,80]

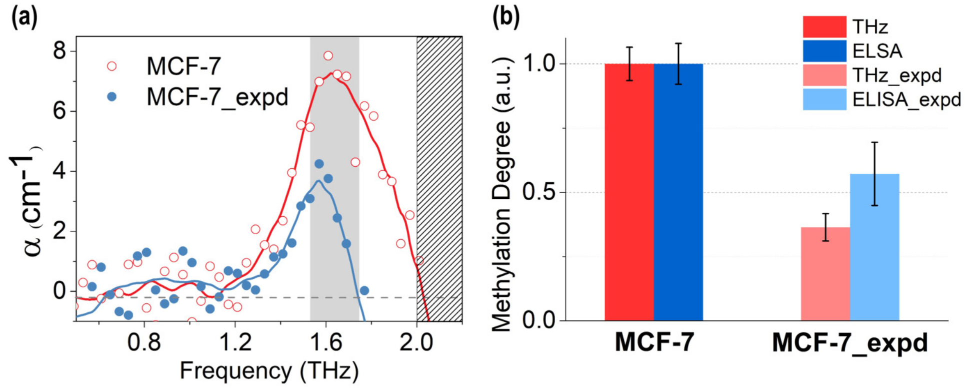

FIG. 9. Demethylation of malignant DNA from breast cancer cell line (MCF-7). (a) Reduction of 1.65-THz resonance peak of methylated DNA by high-power THz radiation passing through a 1.5-THz-centered filter. The amplitude of resonance in the MCF-7 DNA was reduced by 50% after exposure to high-power THz radiation. (b) Good agreement between THz measurements and ELISA results after the THz demethylation of DNA.

Therefore, there is a possibility of improving the cancer treatment outcome by breaking the methyl-DNA bond using THz radiation at the resonance frequency instead of decitabine, which exhibits clinically significant side effects.[81]

The authors have demethylated various malignant DNAs using a high-power THz electromagnetic field.[82] The high-power THz radiation was generated by the nonlinear optical effect of a $LiNbO_3$ crystal driven by a 50-fs, 1-mJ Ti:sapphire regenerative amplifier at a repetition rate of 1 kHz. The irradiating power of the THz field was about 180 $\mu W/cm^2$ after passing through a 1.5-THz-centered bandpass filter. The methylation degree of artificially methylated DNA (M-293T) decreased to below 50% of its initial value, becoming similar to DNA from nonmalignant cell lines (293T).[82] We also demethylated malignant DNA from a breast cancer cell line (MCF-7) and compared the THz-field irradiation results using the enzyme-linked immunosorbent assay (ELISA) method, as shown in Fig. 9.

Titova *et al.* observed a change of gene expression within skin tissue using a similar high-power THz radiation exposure over the entire spectrum up to 2 THz.[22] They demonstrated that THz radiation caused the downregulation of gene expression related to inflammatory skin diseases such as epidermal differentiation complex, nonmelanoma skin cancer, and psoriasis. They argued that THz radiation could be applied in skin disease therapies, including for skin cancer, through a mechanism that modifies the gene expression.

Even though the study of THz radiation therapy is in its infancy, it displays increasing potential in medical applications as we come to better understand the mechanisms behind the phenomena of biomolecular dynamics.

VI. CONCLUSION

Rapid advances in THz technology have seen THz radiation emerge as a potentially useful tool in the field of medicine. The most prominent advantages of THz radiation over other regions of the electromagnetic spectrum are its high sensitivity and specificity to biological molecules and the lack of molecule ionization phenomena. In this perspective, we have summarized the state-of-the-art THz techniques used in medical applications to enhance the sensing capabilities and penetrate deeper within tissues. Many examples of THz cancer imaging studies were discussed, including cases of skin, oral, digestive, breast, and brain cancers. Utilizing the above research, we suggested the development of frozen THz histology microscopes as an initial entry point into the medical market. Attempts to find a cancer-specific signal marker for detection using THz radiation have led to the observation of the molecular resonance of malignant DNA at 1.65 THz. This nonspecific resonance could serve as a universal cancer biomarker. Additionally, by breaking the resonant methyl-DNA bond within malignant DNA using high-power THz radiation, cancers could be cotreated by demethylation, avoiding the unwanted side effects induced by decitabine. Other than the molecular resonance of cancer DNA, the fingerprints or specific signals of biomedical samples being studied should be sought for in applications. This is because the ability to detect them from among biological molecules is a unique advantage of THz radiation along with its nonionizing characteristics. For the detection of weak resonance signals, it is required that THz spectroscopic system should be improved by two or three orders of magnitude in terms of signal-to-noise ratio. THz technology continues to develop rapidly, with devices becoming smaller, less expensive, more accessible, and more powerful. However, extensive clinical trials should be carried out before THz technology can become useful for large-scale implementation in clinics and hospitals In addition, we need passionate people who would be willing to take a risk and accomplish uncertain important achievements to realize THz clinical applications viable in the real world because the principles have been demonstrated and the technologies are maturing.

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