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Research article

Terahertz Reconstructive Imaging: A novel technique to differentiate healthy and diseased human skin

Radhika Srivastava[1], Jennifer Cucalon[2], Aunik K Rahman[*3], Babar Rao[4] and Anis Rahman[3]

[1] Rutgers Robert Wood Johnson Medical School, 675 Hoes Lane West, Piscataway, NJ, USA

[2] American Skin and Cancer Center, 95 First Ave, Atlantic Highlands, NJ, USA

[3] Applied Research & Photonics, 470 Friendship Road, Suite10, Harrisburg, PA 17111, USA

[4] Department of Dermatology, Rutgers Robert Wood Johnson Medical School, 1 Worlds Fair Drive, Somerset, NJ, USA

Corresponding author: Anis Rahman, PhD, 470 Friendship Road, Suite 10, Harrisburg, PA 17111, USA, Tel: +1-717-623-8201; Email: a.rahman@arphotonics.net

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Abstract

Terahertz 3D reconstructive imaging is a novel medical imaging modality that can be used to differentiate of healthy and diseased skin, both ex-vivo and in-vivo. Here, we imaged 21 ex-vivo skin samples using a continuous wave terahertz reflectance reconstructive imaging technique in which the images were rendered by a computer algorithm. The obtained terahertz images showed several differences between healthy and diseased skin. Images of healthy skin showed uniform linear structures with regular pattern, while those of basal cell carcinoma (BCC) showed both linear and lobular structures. Squamous cell carcinoma (SCC) samples also showed pattern dissimilar to the healthy skin images. Similarly, 3D reconstruction images of BCC and SCC demonstrated increased cellularity and disorganization. Future studies incorporating clinical information, spectroscopic analysis, and histology may help connect these patterns observed on imaging to pathological findings. That, along with further optimization of the imaging parameters, can bring this modality to the bedside for effective non-invasive diagnosis.

Key words: terahertz reconstructive imaging, skin, basal cell carcinoma, squamous cell carcinoma

Introduction

With the rising incidence of skin cancer diagnoses [1], clinicians are moving towards non-invasive and cost-effective modalities in order to appropriately diagnose malignant lesions, while minimizing unnecessary biopsies and excisions of benign lesion. Technologies such as electrical impedance spectroscopy (EIS), reflectance confocal microscopy (RCM), and optical coherence tomography (OCT) provide the means for physicians to diagnose cutaneous malignancies while sparing the patient a biopsy. However, each of the above-mentioned techniques have performance limitations as was pointed out previously [2] and as discussed below. In this paper, we present a novel 3D reconstructive imaging technique that uses terahertz radiation (T-ray) for imaging both the surface and sub-surfaces of the skin samples ex-vivo. A depth of ~1 cm may be achieved ad may be tuned via the source power and focusing techniques.

The terahertz (THz) band of the electromagnetic spectrum, ranging from 0.1 THz to ~30 THz [3], is at the junctions of infrared and microwave radiation. It is non-ionizing, therefore, does not impart any radiation damage like X-ray. The longer wavelength of terahertz, relative to other imaging systems, reduces the effect of scattering, a common obstacle of imaging the skin. Different approaches utilizing non-ionizing terahertz radiation have been explored to differentiate between healthy skin and skin cancer. Terahertz pulsed spectroscopy shows statistically significant differences in the absorption coefficient and refractive index between healthy skin and basal cell carcinoma [4]. In both ex-vivo and in-vivo samples, terahertz pulsed imaging shows contrast between healthy skin and basal cell carcinoma that correspond well with histology [4]. However, by using continuous wave reflectance to reconstruct a model of skin, it is possible to differentiate cancerous skin from healthy skin on a cellular level [2] that is not achievable by pulsed imaging.

There are several noninvasive modalities that are available for analyzing the skin; however, many have drawbacks that prevent widespread use. Electrical Impedance Spectroscopy (EIS) is a non-invasive method that utilizes an electrical current to detect changes in cell size, shape, orientation, and structure of cell membranes of the skin [5]. While it is not an imaging modality, it utilizes the impedance pattern of the lesion to generate a score that indicates the likelihood of malignancy [6]. This modality is used primarily in the evaluation of pigmented

lesions. However, the high cost and low specificity of EIS devices are limiting factors. Reflectance Confocal Microscopy (RCM) is a noninvasive imaging modality that utilizes a laser to produce real time in vivo images with higher resolution [5]. RCM is being explored for a wide range of skin disease, including neoplastic and inflammatory processes, and has higher sensitivity and specificity, as well as good correlation with histology. However, the interpretation of RCM images requires rigorous training and experience, as knowledge of the appearance of healthy skin is required to identify pathological changes. Optical Coherence Tomography (OCT) is a noninvasive imaging modality that utilizes infrared light to capture cross sectional images of the skin and superficial vasculature up to 1 mm in depth [6]. OCT is used primarily in the diagnosis of basal cell carcinomas and actinic keratosis. However, the low resolution and low specificity of OCT limits its use. The reconstructive imaging that terahertz technology offers has the capability to overcome the limitations of the previously described noninvasive technologies based on an applied self-cross-checking technique that will be described in the following methodology.

Materials and Methods

Terahertz scanning protocol

Twenty-one ex-vivo human skin samples from 19 consenting patients obtained during routine skin cancer surgery were mounted onto a steel washer with a 5 mm diameter hole. The washer and skin sample were held in a motorized system that moved the sample in the X, Y, and Z planes relative to the fixed terahertz beam. The outer surface of the sample was oriented to face the beam. The TeraSpectra instrument (Applied Research & Photonics) uses a continuous wave terahertz beam that is generated by exposing hyperpolariazable, electro-optically active dendrimer films to a pump laser via a dendrimer dipole excitation mechanism [7]. The generated beam was focused on the skin sample via a reflector. The reflected beam was directed to a detection system, which uses a Newport 2936 Optical Power and Energy Meter to measure the reflected intensity. The sample was moved using high precision motion control, with a resolution of 25 nm in all 3 axes, as it was scanned. A 0.25 mm x 0.25 mm x 0.15 mm area was scanned in each sample. The resulting reflectance was measured and stored in a 3-dimensional matrix. By scanning XY planes at each point on the Z-axis, a 3D matrix of the reflected intensity was recorded, following the modified Beer-Lambert's law as mentioned before. This intensity matrix was subjected to the "gridding with inverse distance to power equations" to generate a lattice which in turn was processed for image formation of the tissue structure. Different color schemas were added to the images for interpretation purposes.

Study sites

Subjects were recruited from a single outpatient dermatology clinic in New Jersey. Subjects were all patients undergoing Mohs micrographic surgery for non-melanoma skin cancer. The co-investigators obtained informed consent from the subjects and performed terahertz imaging of samples.

Sample size

21 lesions were included for an adequate initial assessment.

Subject selection

Inclusion criteria

Capacity to give informed consent

Age > 18 years

Undergoing routine skin excision for biopsy or treatment purposes

Exclusion criteria

No capacity to give informed consent

Not otherwise undergoing skin excision or biopsy

Ex Vivo sample characteristics

Results

Utilizing continuous wave terahertz reflectance reconstructive technique described elsewhere [8], we have generated terahertz images of healthy and diseased skin specimen using the TeraSpectra device. As explained [8], the contrast in the terahertz reconstructive images is generated by the variation of reflectance from different components of skin tissue. Here, a modified Beer-Lambert law is used to describe the reflectance matrix, $R(r)= \varepsilon(r).l(r).\rho(r)$, where, the reflectance is coordinate dependent, which also causes variation in the path length, $l(r)$, and consequently, variation in the coefficient, $\rho(r)$. A 3D reconstructed lattice generated from the measured reflectance matrix (named as the BLR lattice), therefore, yields the characteristic features of the specimen when the lattice is rendered in a suitable color scheme. As the T-ray beam penetrates skin, the energy may be reflected off of a given skin layer by a suitable focusing arrangement. Therefore, the features in the sub-surface layers are identifiable from the reflected intensity, and also from transmitted intensity, as well as from transreflectance responses. In skin tissue, the contrast is generated due to variation in water content, tissue architecture, structural proteins, and other cell constituents. Future experiments will be attempted to correlate terahertz images to histology that will be able to elucidate the tumor nodules, mucinous clefting, and other histologic feature of cancerous skins such as BCC, SCC and lentigo maligna.

Figure 1 (a) exhibits a piece of gauze imaged by terahertz imaging system (0.5 mm x 0.5 mm) via "gridding with inverse distance to power equations," [8] and rendered in a multi-colored format by a commercially available software. It serves as an example of the image-reproducing capability of an actual object by this method. A clear reproduction of the gauze texture indicates the authenticity of images of other specimens. Figure 1 (b) shows a 3D image of a healthy skin tissue (250 μm x 250 μm x 160 μm) rendered in an identical color format as (a). Uniform colors and structures are displayed throughout the

image of healthy tissue. Figure 1 (c) shows a 3D image of a BCC tumor (250 µm x 250 µm x 30 µm), also rendered in the same color format as before. The BCC tumor is evidently illustrated by the disarray of multiple bright colors. Figure 1 (d) shows a 3D image of SCC tumor rendered via an identical color scheme as the BCC. Similar to the BCC tumor in figure 1 (c), the image shows a disarray of multiple colors deviating from the uniform pattern present in healthy skin.

Figure 2 shows six faces of 3D images of healthy skin (row-a) and basal cell carcinoma (row 2), produced by the same terahertz technique and rendered in greyscale. The terahertz images in row-a were obtained from a sample of healthy skin while those in row-b were obtained from a basal cell carcinoma (BCC) sample. The black and white gradient corresponds to the amount of reflection. The spectrometric images of normal skin in row-a show a uniform linear pattern in all six images, as compared to the altered linearity and lobular and linear structures demonstrated in the skin from BCC (row-b). In some images of BCC there is a focal alteration of linearity replaced by lobular and linear structures. This is clearest when the left and right faces of each sample are compared.

Figure 3 compares terahertz images of healthy tissue and a BCC tumor rendered in grey scale. The 3D reconstructed images of these specimens are shown at a higher magnification (50 µm x 50 µm). At this level of amplification normal keratinocytes (corneocytes) are demonstrated in the healthy skin tissue as compared to the increased cellularity and disruption of epidermis in BCC tumor.

Images of SCC tumors exhibited a disruption of the regular linear pattern and presence of lobular structures similar to the BCC tumor images. Fig. 4 compares images of the left face of terahertz images of healthy skin, BCC, and SCC rendered in greyscale. It is evident that the linearity present in the healthy skin is disrupted in both BCC and SCC. This is best visualized in rows 3 and 4, as they demonstrate greater distortion relative to healthy skin.

As argued previously [2], the 3D terahertz image of the healthy skin shows regular cell patterns while the images of BCC sample exhibit irregular and/or agglomerated cell patterns, as is evident from Figures 1, 2, and 3.

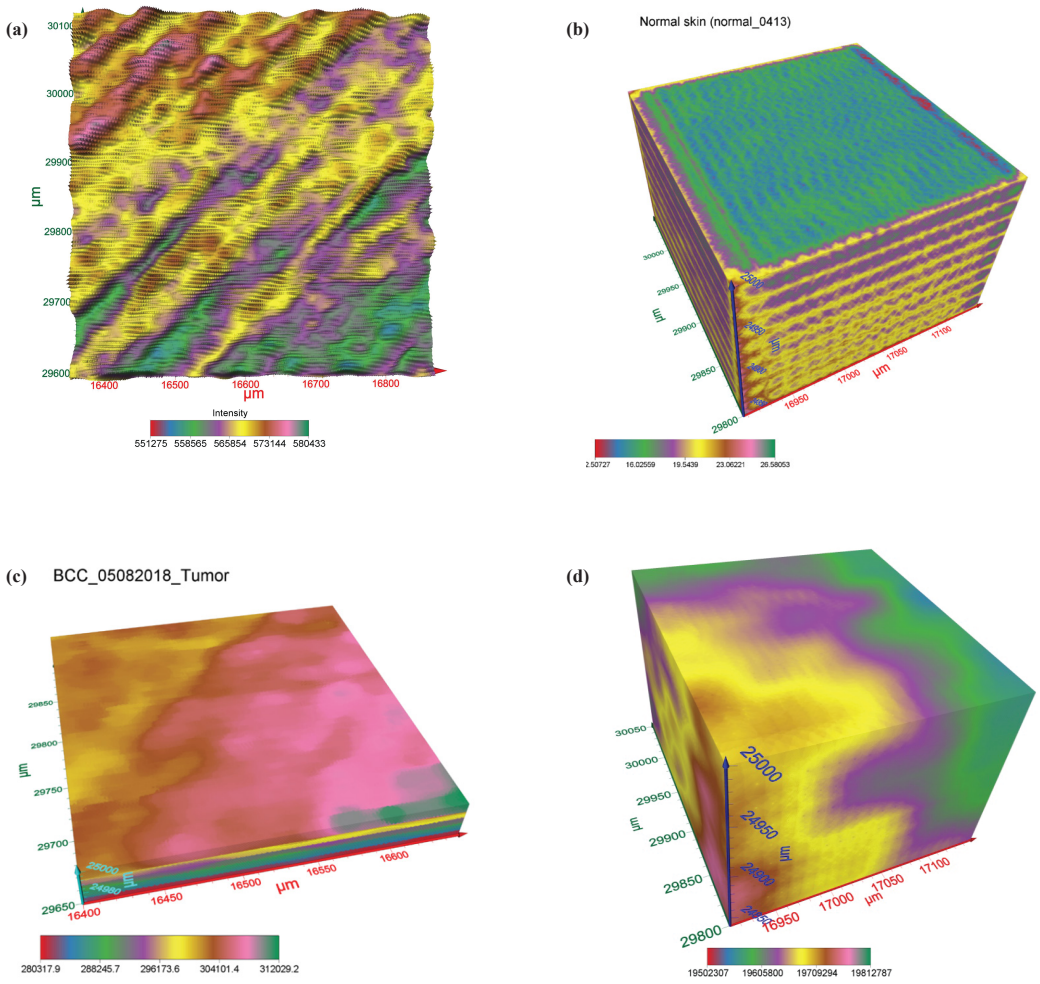


Figure 1. (a) A piece of gauze imaged by terahertz imaging system (0.5 mm x 0.5 mm). (b) 3D image of normal skin (250 µm x 250 µm x 160 µm). (c) 3D image of BCC tumor biopsy (250 µm x 250 µm x 30 µm). (d) 3D image of SCC tumor biopsy (240 µm x 250 µm x 160 µm). All images are identically rendered.

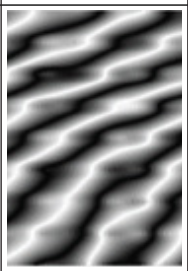
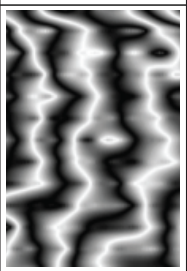
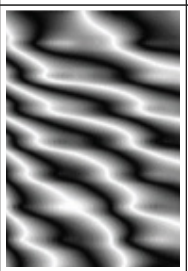
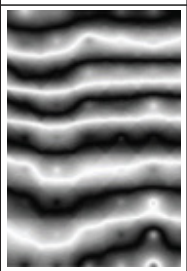
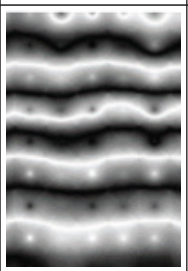
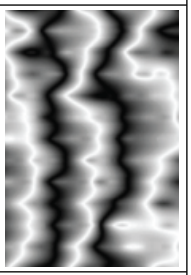
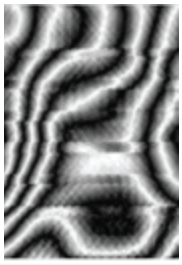
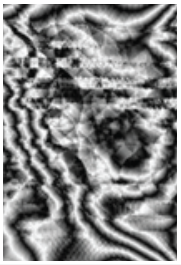
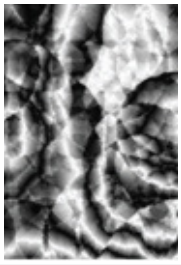
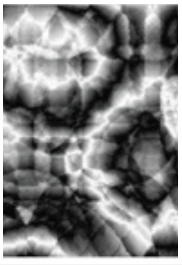
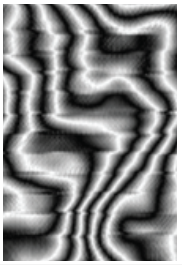
Sample face (area) → Dimension (X×Y×Z)	Back (X×Z)	Bottom (X×Y)	Front (X×Z)	Left (Y×Z)	Right (Y×Z)	Top (X×Y)
(a) Healthy skin Sample: 0102_normal3 Dim: 248µ×260µ×160µ Left and right side show clear indication of healthy tissue						
(b) BCC skin Sample: 1205_bcc Dim: 245µ×260µ×160µ No indication of healthy skin cell pattern						

Figure 2. These images are the six faces of 3D reconstructions of (row-a) Healthy skin and (row-b) basal cell carcinoma. Scanned volume is as shown for the respective specimen.

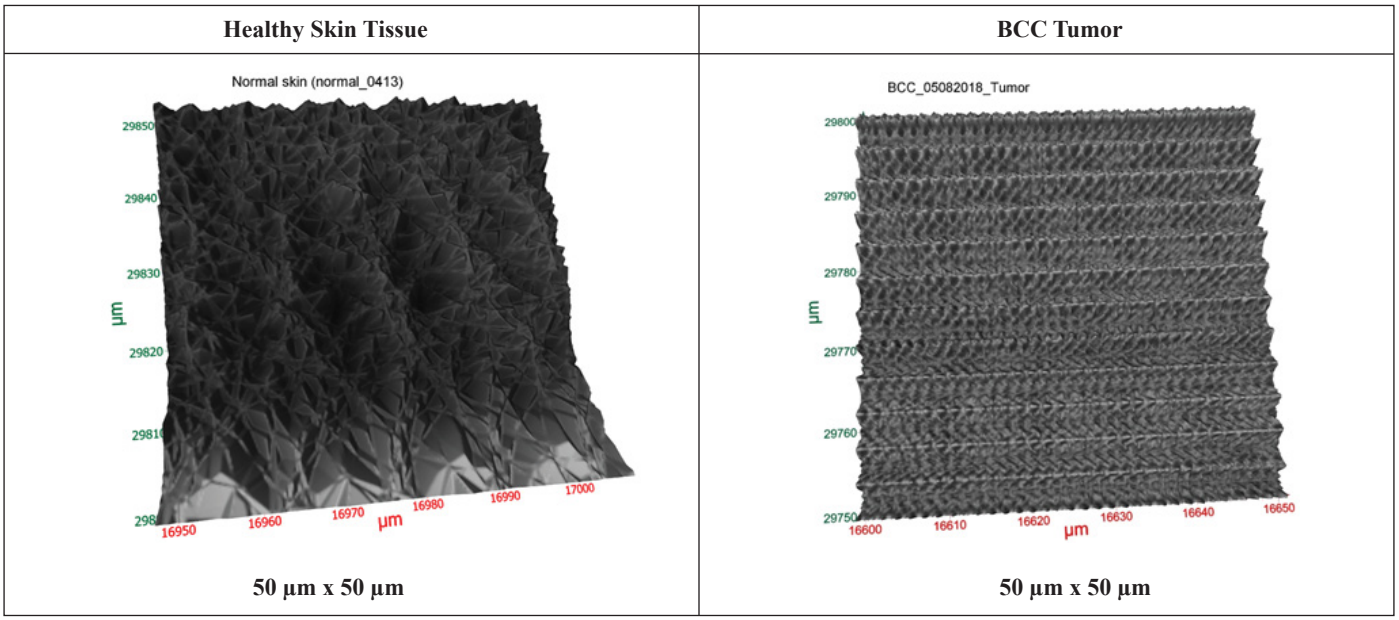


Figure 3. Comparison of terahertz images of healthy tissue vs. BCC tumor, both at a depth of 160 µm.

Discussion

This report describes a novel 3D reconstructive imaging system utilizing terahertz radiation that demonstrates strong potential for non-invasive diagnosis of skin cancer. The reconstructed images display patterns that can differentiate between healthy and diseased skin. It is found that the healthy skin images exhibit a consistent identifiable pattern. Larger experiments may expand on and establish consistent differences between healthy and diseased skin on terahertz imaging. The images of BCC and the SCC skin specimens that incorporate clinical photos and histology alongside terahertz images may be able to correlate differences to known pathological features.

Increasing the power of the incident terahertz beam could improve the quality of images acquired. For terahertz imaging to become a useful diagnostic tool, not only will malignant and benign tissue need to be accurately distinguished, a system must allow large areas (up to several centimeters for BCCs) to to be scanned in-vivo in a reasonable amount of time. This is currently beyond the capability of the system described in this paper, but projects are in the planning for advances in terahertz technology that will help bring terahertz imaging to the clinic and patient bedside.

Conflict of Interest

This research has been initiated by Applied Research and Photonics, Harrisburg, PA, under the leadership of Dr. Anis Rahman. There is no grant involved. The authors declare that they have no conflict of interest.

Acknowledgments

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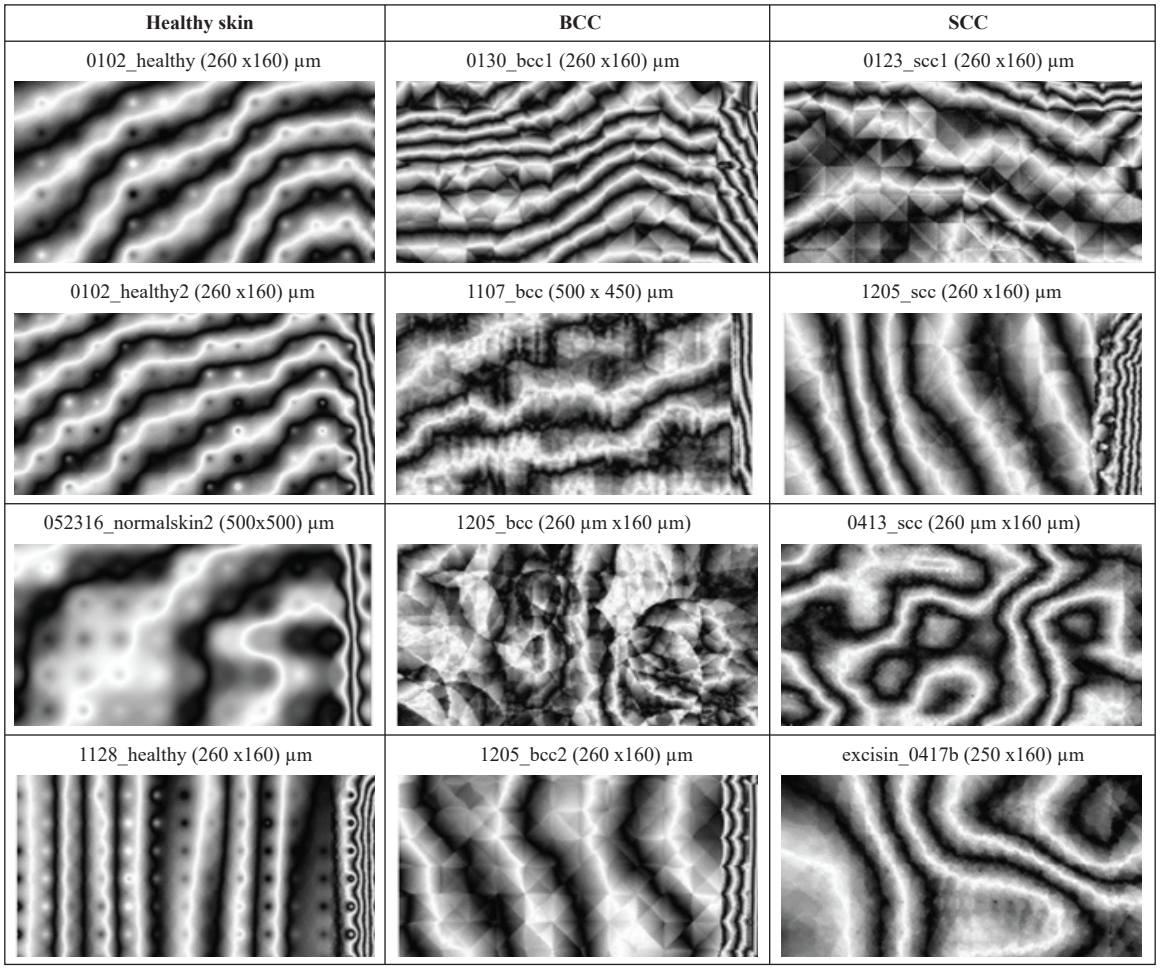

Figure 4. Summary table including images of the left face of terahertz 3D reconstruction of healthy skin, BCC, and SCC. Sample name and dimensions are identified with respective images.

Table 1. Summary of Samples Imaged with the TeraSpectra Device

Patient Number	Age	Sex	Site	Clinical Diagnosis
1	74	F	Nasolabial fold	Basal Cell Carcinoma (BCC)
2	61	F	Ear	BCC
3	78	M	Chest	Healthy
4	73	F	Nose	BCC
5	64	M	Cheek	Squamous Cell Carcinoma (SCC)
6	67	F	Foot	BCC
7	75	F	Leg	SCC
8	85	M	Posterior scalp	BCC
9	91	F	Leg	SCC
10	90	M	Ear	BCC
11	90	F	Nose	BCC
12	78	M	Inferior labial	BCC
13	86	M	Ear	BCC
14	61	M	Forehead	BCC
15	78	F	Nose	SCC
16	58	M	Nose	BCC
17	61	F	Mid upper chest	BCC
18	85	F	Forehead	SCC

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