Research article

Photoacoustic imaging for three-dimensional visualization and delineation of basal cell carcinoma in patients

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ABSTRACT

Background: Photoacoustic (PA) imaging is an emerging non-invasive biomedical imaging modality that could potentially be used to determine the borders of basal cell carcinomas (BCC) preoperatively in order to reduce the need for repeated surgery.

Methods: Two- and three-dimensional PA images were obtained by scanning BCCs using 59 wavelengths in the range 680–970 nm. Spectral unmixing was performed to visualize the tumor tissue distribution. Spectral signatures from 38 BCCs and healthy tissue were compared ex vivo.

Results and discussion: The PA spectra could be used to differentiate between BCC and healthy tissue ex vivo (p < 0.05). Spectral unmixing provided visualization of the overall architecture of the lesion and its border.

Conclusion: PA imaging can be used to differentiate between BCC and healthy tissue and can potentially be used to delineate tumors prior to surgical excision.

1. Introduction

Basal cell carcinoma (BCC) is the most common form of non-melanoma skin cancer. It is characterized by a slowly growing tumor originating from basal cells in the deepest layer of the epidermis, and is most common on the head, neck, and face [1]. The incidence of BCC is increasing worldwide [2], leading to a considerable economic burden on healthcare providers. While the risk of metastasis associated with BCC is low [3,4], local invasion of BCC lesions can lead to devastating destruction of important tissues.

The recommended technique for the diagnosis of BCC is excisional biopsy. Using a 4 mm clinically predetermined margin, excisional biopsies are non-radical in approximately 5% of cases, but the percentage varies depending on the subtype [5]. An alternative technique for the removal of BCC is Mohs surgery, which allows examination of the tumor margins by staged resection and simultaneous histopathological examination [6]. Mohs surgery is considered the most efficient method for the complete removal of high-risk and complicated BCCs. However, the procedure is time consuming and expensive, and dependent on the experience of the physician, which limits its practice to specific cases [7–9].

Preoperative, non-invasive delineation of a tumor could improve patient management and eliminate the need for further excision. Many non-invasive imaging modalities have been used for the in vivo assessment of BCCs, but several have significant limitations. Dermatoscopy is routinely used to examine subsurface tumor characteristics and has facilitated the diagnosis of BCC [10]. However, its penetration depth is limited by optical diffusion, and images cannot be obtained beyond the papillary dermis. Other optical imaging methods, such as confocal microscopy [10–13], and two-photon microscopy [14,15], provide good contrast and resolution, but their penetration depth is also limited. Optical coherence tomography images skin structures down to a depth of about 2 mm and can be used to visualize typical features of skin tumors [15–17]. Although this would be enough to enable visualization of the average BCC, a portion of these tumors, especially the more aggressive subtypes, are thicker than 2 mm [18–20]. High-frequency ultrasound has good resolution at penetration depths greater than those possible with optical imaging, but the contrast is poor as the difference in acoustic impedance between tumors and the surrounding tissue is low [21,22]. Magnetic resonance imaging and positron emission tomography have been used in the assessment of skin tumors [23,24], but they have poor resolution in the skin, are expensive, and are not routinely available for clinical dermatological imaging.

Photoacoustic (PA) imaging is a non-invasive biomedical imaging...
modality that combines the advantages of optical and ultrasound imaging [25]. It can provide high-resolution 3D images of the molecular composition of the tissue. PA imaging employs a laser that emits nanosecond pulses at different wavelengths, typically in the infrared spectral range. The energy of the pulses is absorbed by the tissue, leading to a slight increase in the temperature, which in turn results in ultrasonic signals due to thermoelastic expansion. These ultrasonic waves are collected by an ultrasonic transducer and converted into a multispectral image of the tissue. Although the resolution of PA is not as high as for example optical coherence tomography, PA imaging can provide high-resolution images at a greater depth, making it superior to most optical imaging techniques [26].

So far, PA imaging has mainly been developed experimentally, and only a few studies have been carried out on human skin tumors, mostly high as for example optical coherence tomography, PA imaging can use ultrahigh-frequency ultrasound and PA imaging. Diagnostic ultrasound is used as a guide during PA, and ultrasound images are interleaved with the laser pulses. The system has an ultrasound transducer and a fiberoptic bundle coupled to a 20-Hz tunable laser with a nanosecond pulse width. The laser was operated in the wavelength range 680–970 nm. Two planar light beams, located on either side of the ultrasound linear array, illuminate the skin surface. A 10-mm-thick Aquaflex Ultrasound Gel Pad (Parker Laboratories Inc., Fairfield, NJ, USA) was used to ensure an adequate distance between the laser fibers and the skin line. The photoacoustic waves were detected using an ultrasound linear array transducer MX400 (VisualSonics Inc.), with a central frequency of 30 MHz and bandwidth of 22–55 MHz, which provides axial and lateral resolutions of 50 and 110 μm, respectively. Three-dimensional hybrid images of ultrasound and photoacoustic waves were obtained by scanning the transducer with a linear stepping motor while capturing 2D images, using step sizes between 40 and 500 μm.

2. Materials and methods

2.1. Ethics

The experimental protocol was approved by the Ethics Committee at Lund University, Sweden, prior to the start of the study. The participants were given both verbal and written information about the study and its voluntary nature. Written consent was obtained from all subjects.

2.2. Patients

Forty-one patients, with 44 suspected BCC lesions, were recruited from the Department of Dermatology at Skåne University Hospital in Lund, between September and November 2018, for ex vivo investigation of their lesions. The inclusion criteria were: at least 18 years of age and suspected BCC smaller than 20 × 20 mm. The size of the tumor was limited to allow measurements to be performed using the probe on the tissue. Spectral unmixing was performed to visualize the distribution of the suspected BCC tissue.

| Clinical and histological characteristics of the patients and tumors examined ex vivo. |
|-----------------------------------------------|
| **Patient characteristics** | n | Percentage (%) |
|-----------------------------------------------|
| Sex | Male/female | 18/17 | 51/49 |
| Median age (y) | 70 | Range 52–93 |
| Skin type – Fitzpatrick scale (I–VI) | I/II | 5/30 | 14/86 |
| Diabetes mellitus | Type 1/type 2/no | 1/5/29 | 3/14/83 |
| Hypertension | Yes/no | 15/20 | 43/57 |
| Stroke | Yes/no | 5/30 | 14/86 |
| Smoking | Yes/no/previous | 4/24/7 | 11/69/20 |
| Histological characteristics | Superficial/nodular/morpheiform | 6/22/10 | 16/58/26 |
| Radical excision | Yes/no | 35/3 | 92/8 |
| Minimum margin stated | Yes/no | 18/20 | 47/53 |

2.3. Photoacoustic imaging equipment

A Vevo LAZR-X multimodal imaging system was used (FUJIFILM VisualSonics Inc., Toronto, ON, Canada), which allows examination using ultrahigh-frequency ultrasound and PA imaging. Diagnostic ultrasound is used as a guide during PA, and ultrasound images are interleaved with the laser pulses. The system has an ultrasound transducer and a fiberoptic bundle coupled to a 20-Hz tunable laser with a nanosecond pulse width. The laser was operated in the wavelength range 680–970 nm. Two planar light beams, located on either side of the ultrasound linear array, illuminate the skin surface. A 10-mm-thick Aquaflex Ultrasound Gel Pad (Parker Laboratories Inc., Fairfield, NJ, USA) was used to ensure an adequate distance between the laser fibers and the skin line. The photoacoustic waves were detected using an ultrasound linear array transducer MX400 (VisualSonics Inc.), with a central frequency of 30 MHz and bandwidth of 22–55 MHz, which provides axial and lateral resolutions of 50 and 110 μm, respectively. Three-dimensional hybrid images of ultrasound and photoacoustic waves were obtained by scanning the transducer with a linear stepping motor while capturing 2D images, using step sizes between 40 and 500 μm.

2.4. Ex vivo setup and measurements

The skin lesions were surgically removed under local anesthesia, according to standard clinical procedure. Two Prolene 6-0 sutures were sewn to each end of the lesion, and it was then mounted in a 100 × 70 × 50 mm Perspex container, filled with buffered saline solution (Fig. 1A). The bottom of the container was covered with an ultrasound-attenuating material. A combined photoacoustic and ultrasound setup was used, as shown in Fig. 1B. The transducer was mounted on an adjustable arm (Mounting Accessory, GCX Corporation, Petaluma, CA, USA) to avoid motion artifacts caused by the examiner. The transducer was driven by a stepping motor (VisualSonics Inc., Toronto, Canada) allowing 3D images to be obtained.

2.5. Spectral signature of BCCs

To obtain the mean photoacoustic signature of all tumors, four spectral scans were performed on each lesion: three in different parts of the tumor, and one outside the lesion in healthy tissue, as a reference. The first of the three scans of the tumor was chosen for further analysis if the signal-to-noise ratio was deemed adequate at visual inspection. If the signal quality was suboptimal, the other two scans were also analyzed and the one with best quality was selected for further use. This resulted in 59 PA images collected at different wavelengths (680–970 nm in steps of 5 nm) giving each 'pixel' of the ultrasound image a spectrum dependent on the optical properties of the tissue. It was hypothesized that these spectra could provide a fingerprint of typical BCC tissue.

2.6. Multiwavelength 3D scan

To obtain the spectral signals for the whole ex vivo tissue and to be able to perform spectral unmixing, a multiwavelength 3D scan was performed using the same 59 wavelengths (680–970 nm, in steps of 5 nm). The step length between each 2D image was 500 μm. The scanning time for a multiwavelength 3D scan was approximately 4 min.

2.7. Histopathology

After ex vivo imaging, the lesion was placed in formalin and sent for histological analysis using standard staining with hematoxylin and eosin (H&E).
2.8. Data analysis

All measurements were analyzed and assessed using VisualSonics Vevo LAB 3.1.0 software for data processing and storage. With the help of this software, regions of interest (ROIs) were defined in the ultrasound image. Freehand ROIs were drawn only on the most certain central part of the lesion to get a signal derived from the tumor tissue. The same was done from the most certain part of the healthy tissue outside of the lesion and was used as a reference. Each ROI could then be translated into the mean PA spectral signal of the corresponding area in the software, making it possible to compare the tumor signal with the signal from the surrounding healthy tissue.

The spectral signals from the tumors and healthy tissue were exported to MATLAB R2017b (MathWorks Inc., Natick, MA, USA) for further calculations and graph drawing. To calculate the mean signal for all the lesions, the signals were first min-max normalized into the 0–1 range. Graphs were created representing the mean of all the lesion spectra and the healthy tissue spectra.

2.9. Spectral unmixing

In addition to multiwavelength 3D scans, an imaging technique known as spectral unmixing was employed. The resulting mean PA tumor spectrum from the 38 lesions were used as the endmember spectrum. A linear spectral unmixing approach minimizing the mean squared error was then performed in every pixel for all collected 2D images, producing false-colored images that were overlaid the ultrasound images, mapping out the probable spatial distribution of BCC tissue [37]. Due to the complexity of the chromophoric composition of BCC, this analysis was thus based on the overall spectral dissimilarities between BCC and healthy tissue instead of identifying individual chromophores.

2.10. Statistical analysis

Comparison of the normalized spectral signals were analyzed using two-way analysis of variance (ANOVA) for repeated measures followed by the Sidak multiple comparison test. Significance was defined as: $p < 0.05$ (∗) and $p > 0.05$ (not significant, n.s.).

3. Results

3.1. Spectral signatures

A clear difference was seen between the mean spectra from BCCs and healthy tissue ex vivo. This difference was statistically significant ($p < 0.05$) in the wavelength range 760–945 nm (Fig. 2). Individual spectra could vary, as indicated in the range, and no clear difference between the various BCC subtypes could be found. For instance, at 850 nm, mean tumor signal was 0.31 (range 0.16–0.51) and healthy tissue 0.20 (range 0.05–0.43). The difference between the two groups remained statistically significant also when using alternative methods for normalization, such as normalization at 920 nm.

The gradual change in the PA spectrum, from lesion to normal tissue, was investigated by defining several small ROIs in a row, starting at the center of the tumor and extending out into healthy tissue (Fig. 3).

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Fig. 1. Photographs of the ex vivo examination setup. (A) An excised lesion suspended in a saline solution. (B) The PA probe attached to an adjustable arm with the stepping motor, used for the examinations.

Fig. 2. The mean PA spectra obtained from BCCs and the surrounding healthy tissue from ex vivo measurements. The dispersion (± one standard deviation) is indicated by the shaded areas. A clear difference can be seen in the spectral signatures of the BCCs and healthy tissue ($p < 0.05$ for 760 to 945 nm, $n=38$).
This provides further evidence that the PA signal could be used to differentiate cancerous tissue from healthy tissue.

3.2. Multiwavelength 3D scanning and spectral unmixing

Multiwavelength 3D scanning was performed over the whole excised lesion, providing a map of the overall lesion architecture. To obtain more information on BCC tissue distribution in the lesion, spectral unmixing was performed on the multiwavelength recordings using the mean absorption spectrum for all 38 tumors. Fig. 4 shows a spectrally unmixed 3D sequence of a nodular BCC lesion and Fig. 5a superficial BCC, illustrating how this can be used to differentiate the tumor tissue from the surrounding healthy tissue.

4. Discussion

Photoacoustic imaging constitutes a new optical technique that can be used to obtain real-time 2D and 3D images, with high resolution and depth, for the evaluation of skin tumors. The main strength of PA imaging is its ability to image molecular changes, and thus differentiate healthy from diseased tissue. The high resolution and imaging depth may make it possible to determine the tumor borders in three dimensions. However, mainly preclinical studies have been performed to date. In this study, we have demonstrated the feasibility of PA imaging in differentiating between BCC and healthy tissue by analyzing the spectral signatures. Furthermore, using this information for spectral unmixing, the distribution of tumor tissue could be visualized. This shows promise for future presurgical definition of the tumor, but further development of the spectral unmixing algorithms is needed before this can be studied.

So far, only two other research groups have used PA imaging to study BCCs [27,30,31,38]. A research group at the National Skin Center in Singapore has shown that PA can be used to visualize and measure the depth and length of BCCs in vivo in a small group of patients (Supplementary Table S1 in [31]). They performed 3D reconstructions using 10 wavelengths between 700 and 900 nm with an iVision 512-echo opto-acoustic imaging system (iThera Medical, GmbH, Munich, Germany) [27,31]. The majority of the patients in their study manifested with pigmented BCCs, and the tumor depth and length were obtained by calculating the distance between the non-baseline values of the melanin signals after spectral unmixing. While pigmentation of BCCs is seen in 50% of Blacks, Hispanics, and Japanese, only 6% of...
BCCs are pigmented in Caucasians [39]. The patients in the present study were defined as Fitzpatrick skin type I or II (i.e. fair-skinned), and none had a pigmented BCC. Most clinical in vivo and ex vivo studies using PA have been performed on melanoma lesions [28,29,34,36,40]. Melanoma lesions contain higher amounts of melanin, which is an endogenous chromophore with a known absorption spectrum [41].

Photoacoustic imaging relies on the absorption of light in the tissue by chromophores, and the degree of absorption varies with the concentration of chromophores in the tissue. The difference in spectral signatures between BCCs and healthy tissue thus expectedly provides an indication that the molecular compositions are different. The lack of pigmentation in the BCCs investigated in the present study suggests that melanin alone is not responsible for the difference in the spectral signatures of tumors and healthy tissue. The cellular origin of BCC has not been completely elucidated, but it has been reported that BCC can arise from multiple epidermal and follicular compartments [42,43]. Cytokeratin is expressed in all types of epithelial cells, and is often used as an immunohistological marker for non-melanoma skin tumors [42,44]. In addition, BCCs often contain arborizing blood vessels. These features, together with others, may explain the changes in the spectrum seen in the wavelength interval 745 – 965 nm. A larger number of wavelengths (59) and a broader spectral range (680 – 970 nm) were used in the present study than in previous studies. This provides a broader view of the molecular composition of the tissue, increasing the probability of finding differences between cancerous and healthy tissue.

The PA examinations in the present study were performed on surgically excised BCCs. This provided high-resolution spectra, free from motion artifacts and other sources of interference. One of the most important tasks in the translation of the PA technique from the ex vivo to the in vivo setting is the reduction of motion artefacts. We have recently published a paper describing a setup allowing for in vivo 3D PA scanning in patients [45]. In an effort to reduce motion artefacts, the patients were examined lying down, and the area to be examined was stabilized with a vacuum pillow. The transducer was mounted on an adjustable arm and moved by a stepping motor, instead of using a handheld transducer. A few examinations have been carried out on BCCs in vivo with this setup and the results are encouraging (data not shown).

The spectral signal was found to change distinctly at the border when moving from the center of the tumor to the surrounding healthy tissue. This not only confirms that there is a difference between the signals from a BCC and healthy tissue, but also indicates the possibility of using this modality to define tumor borders in the future. With the aid of machine-learning techniques, it may be possible to define the tumor margins, avoiding operator subjectivity, learning curves and variations in the examiner’s assessment. To identify and mark the tumor border, it would be necessary to develop a probe that is capable of this, as this does not exist today. A first step toward the implementation of PA in the clinical setting, could be to excise the tumor in the routine way, and then immediately scan the lesion ex vivo to determine whether it has been radically removed. This would be faster than conventional Mohs surgery. Further developments and studies on a larger number of patients with different kinds of skin tumors will be required before the method can be implemented in the clinic.

One limitation of the present study was that it was not possible to separate the different sub-types of BCCs due to the limited sample size. There was some interindividual variability in the spectra obtained from the lesions, which could have been partially due to different subtypes of BCCs. Further studies are required on larger groups of histologically different BCCs to investigate the spectra for specific subtypes of BCCs. Surgery involves external trauma to the body, and autolysis is initiated a certain time after excision, resulting in the release of metabolites into the tissue and edema. This could affect the results, however the time between excision and measurement was short, which makes this improbable. Furthermore, the spectrum from the tumor tissue was compared to that of surrounding healthy tissue that has experienced the same trauma, which should eliminate this source of error.

In summary, the spectral signatures from BCCs and healthy tissue were found to be statistically significantly different. Spectral unmixing could be used to visualize the probable distribution of BCC tissue in three dimensions. Our findings provide further evidence of the potential of this new imaging method in guiding surgical intervention to achieve more precise excision with better clearance, reducing the need for repeated surgery. It may also be possible to shorten the duration of traditional Mohs surgery by using PA imaging instead of histopathological examination of the excised lesion. Further studies are necessary to develop the technique so that it can be used to identify the tumor margins prior to surgery.

Funding source

All sources of funding should also be acknowledged and you should declare any involvement of study sponsors in the study design; collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication. If the study sponsors had no such involvement, this should be stated.

Declaration of Competing Interest

A conflicting interest exists when professional judgement concerning a primary interest (such as patient’s welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry). It may arise for the authors when they have financial interest that may influence their interpretation of their results or those of others. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

Acknowledgements

This study was supported by the Swedish Government Grant for Clinical Research (ALF), Skåne University Hospital (SUS) Research Grants, Skåne County Council Research Grants, Lund University Grant for Research Infrastructure, the Swedish Cancer Foundation Crown Princess Margaret’s Foundation (KMA), the Foundation for the Visually Impaired in the County of Malmöhus, The Nordmark Foundation for Eye Diseases at Skåne University Hospital, Lund Laser Center Research Grant, Inga Brit and Arne Lundberg Research Foundation, Carmen and Bertil Regné Foundation and the Swedish Eye Foundation. The authors would like to thank John Albinsson, Josephin Andersson, Bo Baldetorp, Cassandra Hennström, Katarina Lundqvist, Helen Sheppard and the surgical staff at the Department of Dermatology in Lund for valuable help with this project.
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